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Postconcussive Symptoms, PTSD, and Disease Burden in U.S. OEF and OIF Veterans: A Mediational Model

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POSTCONCUSSIVE SYMPTOMS, PTSD, AND DISEASE BURDEN IN U.S. OEF AND OIF VETERANS: A MEDIATIONAL MODEL

by

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Abstract

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The most common psychological and cognitive sequelae associated with deployments to Afghanistan (OEF) and Iraq (OIF) are mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD). Each of these injuries places Veterans at risk for long-term health problems. One long-term problem associated with mTBI is the development of persistent, postconcussive symptoms, although relations between postconcussive symptoms, PTSD, and objective and subjective health indices have not been empirically explored. This study examined whether PTSD mediates relations between persistent, postconcussive symptoms related to mTBI and two indices of medical disease burden: the number of disease categories positive for a diagnosis, or system disease burden, and total number of physical diagnoses, or cumulative disease burden. The study also examined whether PTSD mediates relations between postconcussive symptoms and self-reported physical health functioning. Participants were 573 OEF/OIF Veterans screened in a VA primary care clinic. Medical records of participants seeking VA health care were reviewed for a history of mTBI, postconcussive symptoms, and physician diagnoses, which were used to derive system and cumulative disease burden variables. Evidence suggests that PTSD did not mediate relations between postconcussive symptoms and cumulative disease burden. These results were also supported after removing nonspecific symptoms from the postconcussive and PTSD symptom variables. These findings join an emerging body of literature suggesting that the residual effects of

TBI have a direct, lasting impact on Veterans' physical health above and beyond the effects of PTSD.

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Chapter 1

Introduction

The evolving nature of warfare as characterized by frequent exposure to blasts and explosions during routine military operations (e.g., Gondusky & Reiter, 2005) places Veterans of Operations Enduring Freedom (OEF) in Afghanistan and Iraqi Freedom (OIF) at increased risk for a myriad of psychological and cognitive sequelae. Although unseen, these sequelae, most notably mild traumatic brain injury (mTBI), also commonly referred to as concussion (Hoge, Goldberg, & Castro, 2009), and posttraumatic stress disorder (PTSD), often have a sizable impact on Veterans' psychosocial and physical health. Denoting a TBI as mild depends largely on the time course of symptoms experienced in the immediate aftermath of sustaining the injury. Individuals sustaining mTBI typically have loss of consciousness lasting no more than 30 minutes after the initial injury or posttraumatic amnesia lasting no more than 24 hours after the injury (Kay et al., 1993). Prevalence estimates suggest that between 15% and 19% of OEF/OIF Veterans sustained an mTBI during deployment (Hoge et al., 2008; Tanielian & Jaycox, 2008). Consistent with these estimates, efforts to screen for mTBI among all returning OEF/OIF Veterans seeking services within the Veterans Affairs (VA) health care system (Department of Veterans Affairs, 2007) indicate that approximately 21% of Veterans experienced a probable mTBI during deployment and continue to experience persistent, postconcussive symptoms (e.g., headaches, dizziness, sensitivity to bright light) associated with the injury (Carlson et al., 2010). More variable rates of PTSD have been reported with 12% to 39% of OEF/OIF Veterans either enrolled in or actively seeking VA health care screening positive for PTSD (e.g., Erbes, Westermeyer, Engdahl, &

Johnson, 2007; Jakupcak, Luterek, Hunt, Conybeare, & McFall, 2008). However, these injuries are not mutually exclusive – between 26% and 44% of OIF Veterans screening positive for mTBI also screen positive for PTSD (Brenner et al., 2010; Hoge et al., 2008). The high rates of mTBI and PTSD carry significant implications for the long-term readjustment of this Veteran cohort, especially in light of a growing body of literature linking both mTBI and PTSD with poorer health.

MTBI, Postconcussive Symptoms, and Health

By definition, mTBI involves some physiological injury to the brain whether as a result of barotrauma, or damage caused by rapid changes in atmospheric pressure, or blunt trauma (Taber, Warden, & Hurley, 2006). MTBI can be differentiated from more severe TBIs based on the time course and, thus, severity of symptoms experienced in the immediate aftermath of the injury. Specifically, loss of consciousness for more than 30 minutes or posttraumatic amnesia for more than 24 hours following the injury is suggestive of moderate or severe TBI, and typically requires immediate medical attention, while individuals with mTBI may not lose consciousness or have any memory loss for the injury (Alexander, 1995; Hoge et al., 2009). Consequently, individuals sustaining an mTBI may not seek or receive immediate medical care following the injury. Indeed, a large, population-based survey of OEF/OIF Veterans conducted by the RAND Corporation (Tanielian & Jaycox, 2008) suggested that over half of Veterans reporting a history of deployment-related TBI had never been evaluated by a clinician for possible brain injury.

Clinically evaluating whether a historical event qualifies as an mTBI can be difficult given that alterations in consciousness or loss of memory for events can also reflect acute stress reactions rather than brain injury (Bryant, 2008, Hoge et al., 2009). Perhaps the most reliable way to evaluate an individual for TBI is to evaluate the person at the scene of the injury or in a medical setting (e.g., emergency room) immediately following the injury using indices like the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), which assesses an individual's alertness via motor responsiveness, verbal performance, and eye opening ability; an mTBI is usually defined as a score of 13-15 on the GCS (Hoge et al., 2009). Possible scores on the GCS range from 3 to 15 where lower scores are associated with less responsiveness. The GCS is typically only administered to patients in emergency departments or other medical settings in the acute post-injury phase, however, and many Veterans experiencing TBI-related injury events during deployment may not receive this level of evaluation in the war-zone. In an effort to improve identification of and delivery of medical services for mTBI, the U.S. military implemented a policy requiring that all Veterans within 100 meters of a blast be screened for mTBI in theatre (see Bryant, Castro, & Iverson, 2012, for review). Veterans deemed to have experienced a concussion are subsequently placed on temporary profile for 72 hours prior to returning to duty in an effort to reduce the likelihood of exposure to additional head injuries during the acute post-injury period. Nevertheless, even without proper identification and treatment, many Veterans with a history of untreated, deployment-related TBI, particularly those who sustained an mTBI, will naturally recover from their injuries within a matter of weeks or months without any form of intervention (see Alexander, 1995, for a review of the natural history of mTBI). For others, mTBI is associated with functional impairment long after the injury and may facilitate the onset of a number of degenerative health problems.

Why some individuals experience poor long-term outcomes following mTBI remains a topic of considerable scientific and clinical debate. Some researchers point to the fact that a wide range of injuries of varying severity may fit the definition of mTBI (e.g., Iverson, 2012). For example, a subtype of mTBI referred to as “complicated” mTBI involves the presence of a brain lesion or depressed skull fracture in addition to the traditional period of altered consciousness (Williams, Levin, & Eisenberg, 1990), and complicated mTBI may place individuals at risk for worse long-term functional outcomes (Iverson, 2012). More recent advances in neuroimaging have also led to the discovery that, for some individuals, mTBI is associated with damage to white matter networks in the brain, and frontotemporal brain regions are thought to be highly susceptible to deformation in mTBI (Bigler & Maxwell, 2012). In all likelihood, though, poor outcome following mTBI is probably shaped by interacting biological, psychological, and social factors. In screening for TBI post-deployment, the VA and Department of Defense created instruments, including the VA TBI Clinical Reminder (Department of Veterans Affairs, 2007), that aim to screen individuals not only on the basis of sustaining probable TBIs during deployment but also on the basis of experiencing ongoing symptoms (Bryant et al., 2012). That is, current efforts within the military and VA health care system to screen individuals for mTBI are geared towards identifying this subset of individuals experiencing poor long-term outcomes following mTBI.

Poor outcomes following mTBI may include, but are by no means limited to, health problems. Using a community-dwelling sample of individuals with a history of TBI and a comparison group of individuals with no history of brain injury, Findler, Cantor, Haddad, Gordon, and Ashman (2001) observed that individuals with a history of mTBI reported more health problems and generally reported worse health functioning than individuals in the non-injured comparison group. More recently, a literature review conducted by the Institute of Medicine concluded that there is evidence suggestive of an association between mTBI with loss of consciousness at the time of injury and several long-term neurologic outcomes such as unprovoked seizures, dementia, and parkinsonism (Ishibe, Wlordarczyk, & Fulco, 2009). While the association between mTBI and neurologic problems likely stems from structural brain damage incurred at the time of the injury, persistent, postconcussive symptoms associated with the mTBI may impact health via different mechanisms.

The terms mTBI and postconcussive symptoms are often, although inappropriately, used interchangeably. Whereas mTBI refers to a historical event, postconcussive symptoms refer to the active sequelae of a past TBI (Hoge et al., 2009). The structure of postconcussive symptoms remains a topic of debate. Even so, postconcussive symptoms are widely thought to fit into 3 distinct clusters, including somatic/sensory, cognitive, and affective symptoms. Caplan et al. (2010) found support for these 3 clusters in a factor analytic study of the Neurobehavioral Symptom Inventory (NSI; Cicerone & Kalmar, 1995), a self-report measure of postconcussive symptoms. Postconcussive symptoms assessed on the NSI and their respective symptom clusters are listed in Table 1.

OEF/OIF Veterans with a history of deployment-related mTBI are at increased risk of experiencing a variety of somatic and postconcussive symptoms, including headaches, dizziness, balance problems, and tinnitus (e.g., Hoge et al., 2008; Polusny et al., 2011). Compared to individuals with moderate to severe TBI, individuals sustaining

Table 1

Postconsussive Symptoms Assessed by the Neurobehavioral Symptom Inventory (NSI)

Somatic/Sensory	Cognitive	Affective
Dizziness		
Loss of Balance		
Poor Coordination/Clumsy		
Nausea		
Vision Problems/Blurring		
Sensitivity to Light		
Hearing Difficulty		
Sensitivity to Noise		
Numbness in Parts of Body		
Change in Taste/Smell		
Change in Appetite		
	Slowed Thinking	
	Poor Concentration	
	Forgetfulness	
	Decision-Making Difficulty	
		Headache
		Anxiety
		Irritability
		Fatigue/Loss of Energy

(*table continues*)

Table 1. (continued)

Postconsussive Symptoms Assessed by the Neurobehavioral Symptom Inventory (NSI)

Somatic/Sensory	Cognitive	Affective
		Disturbed Sleep
		Poor Frustration Tolerance
		Depression

Note. Structure of symptoms based on results of Caplan et al. (2010).

an mTBI tend to report more postconcussive symptoms (Belanger, Kretzmer, Vanderploeg, & French, 2009), which may result in long-term functional impairment. For instance, Emanuelson, Andersson Holmkvist, Björklund, and Stålhammar (2003) reported that, in a population-based sample of Swedish civilians with mTBI, higher rates of postconcussive symptoms were associated with worse self-reported health functioning. Interpreting these relations can be difficult, however, since postconcussive symptoms are often highly comorbid with psychological conditions like PTSD, a well-known risk factor for poor health outcomes (e.g., Green & Kimerling, 2004).

Given that mTBIs usually occur under potentially traumatic, life-threatening conditions, mTBI and postconcussive symptoms may leave individuals at increased risk for developing PTSD by taxing cognitive resources necessary to successfully accommodate trauma memories (Bryant, 2008). So, in addition to shared causality, there may be an interaction effect between mTBI, postconcussive symptoms, and PTSD such that more postconcussive symptoms following mTBI increase susceptibility to PTSD. Several lines of research in civilian populations support the position that postconcussive symptoms increase risk for PTSD. For instance, Bryant and Harvey (1999) reported that, in a sample of motor vehicle accident survivors, mTBI patients with PTSD endorsed more postconcussive symptoms than mTBI patients without PTSD. Similarly, Feinstein, Hershkop, Jardine, and Ouchterlony (2000) found statistically significant relations between PTSD symptoms and postconcussive symptoms, including headaches, fatigue and dizziness, in a sample of individuals attending an outpatient head injury clinic. Together, these studies suggest that, in addition to health risks associated with neurological damage resulting from mTBIs, persistent postconcussive symptoms may indirectly impact health by increasing patients' risk for PTSD.

PTSD and Health

The association between PTSD and adverse health consequences is well-documented. In an early review of this topic, Friedman and Schnurr (1995) concluded that PTSD was associated with several categories of health outcomes, including self-reported health outcomes, health care utilization, and morbidity, or disease prevalence. Since the publication of this review, an extensive literature has emerged providing additional support for Friedman and Schnurr's original conclusions, although the bulk of this literature has focused on the association between PTSD and self-reported health. At the time of their original review, Friedman and Schnurr noted that, in terms of self-reported health outcomes, only one study had explored the association between PTSD and health in a non-Veteran sample. Over the last decade, a number of studies have convincingly demonstrated that PTSD is independently associated with self-reported health functioning and physical conditions in both Veteran samples and a variety of non-Veteran samples, including spousally bereaved individuals (Silverman et al., 2000), homicidally bereaved individuals (Williams, Burke, McDevitt-Murphy, & Neimeyer, 2012), medical patients (Ouimette et al., 2004), and college students (Lawler, Ouimette, & Dahlstedt, 2005).

A number of additional studies published since Friedman and Schnurr's 1995 review have also bolstered the conclusion that PTSD is independently associated with disease morbidity. These studies included diverse, trauma-exposed samples such as World War II (Schnurr, Spiro, & Paris, 2000) and Vietnam Veterans (Boscarino, 1997) as well as non-Veteran samples of female Medicaid recipients (Seng, Clark, McCarthy, & Ronis, 2006). Several possible mechanisms may explain these associations, including higher rates of negative health habits like heavy drinking among individuals with PTSD (see Chilcoat & Menard, 2003, for a review of issues related to PTSD and substance use disorder comorbidity). PTSD is also associated with biological changes in the hypothalamic-pituitary-adrenal (HPA) axis (Yehuda, 2001) that may at least partially account for the relation between PTSD and physical health as reflected by higher rates of medical diagnoses. Yet another possibility, especially in relation to self-reported somatic complaints and health functioning, is that PTSD promotes heightened anxiety sensitivity (e.g., Taylor, 2004) such that physical sensations are inaccurately interpreted as indicative of more serious health problems.

Associations between PTSD and poor health have also been found in OEF/OIF Veterans. In a sample of OIF Veterans assessed 1 year after deployment, Hoge, Terhakopian, Castro, Messer, and Engel (2007) reported that Veterans screening positive for PTSD endorsed higher rates of several self-reported somatic symptoms including back pain, chest pain, and digestive problems. Vasterling et al. (2008) found evidence suggestive of an association between PTSD and more self-reported health complaints in a non-treatment-seeking sample of OIF Veterans, an association that was independent of the effects of alcohol use or other health risk behaviors. Findings suggesting that the association between PTSD and self-reported physical health is independent of the effects of heavy drinking were further supported in a sample of OEF/OIF Veterans seeking VA health care (McDevitt-Murphy et al., 2010). Using medical diagnoses given by VA clinicians to objectively assess relations between PTSD and health among OEF/OIF Veterans, Andersen, Wade, Possemato, and Ouimette (2010) reported that PTSD was associated with an increased risk of developing nervous system, circulatory system, digestive system, and musculoskeletal system diseases. In an extension of this work, Possemato, Wade, Andersen, and Ouimette (2010) found that PTSD was associated with an increased risk of diagnoses across multiple medical categories (e.g., circulatory, digestive, musculoskeletal), which they termed "system disease burden." They further reported that PTSD was associated with an increased risk of having more medical diagnoses, regardless of category, a health index they termed "cumulative disease burden." Each of these indices of disease burden offers informative though different perspectives on the means by which postconcussive symptoms, PTSD, or other conditions affect health. For example, system disease burden provides a measure of the extent to which the health effects of some condition (e.g., postconcussive symptoms, PTSD) are *pervasive* across disease types and physical systems. Cumulative disease burden, on the other hand, provides a measure reflective of the *magnitude* of the impact conditions like persistent postconcussive symptoms or PTSD have on multimorbidity, or the co-occurrence of medical conditions within a given person.

Together, these studies highlight the link between PTSD and increased health problems. The link between PTSD and health problems extends to OEF/OIF Veterans with several recent studies demonstrating associations between combat-related PTSD and self-reported health and morbidity in this Veteran cohort. However, the role of mTBI in these relations remains largely unknown. Despite the paucity of research on relations between mTBI, PTSD, and health, some recent evidence suggests that PTSD may partially mediate relations between mTBI and health.

MTBI, PTSD, and Health

Veterans with a history of mTBI, persistent postconcussive symptoms, and PTSD often report a variety of health complaints, a clinical presentation that some researchers have described as "postdeployment multi-symptom disorder" (Walker, Clark, & Sanders, 2010). Indeed, neural pathways typically associated with mTBI and PTSD are also commonly implicated in the experience of chronic pain (Otis, Fortier, & Keane, 2012), which may exacerbate overall health complaints and limit health-related quality of life. Generally speaking, though, recent efforts to explore associations between mTBI, PTSD, and poor health among civilian and military samples have yielded mixed findings. In a national sample of individuals hospitalized after a traumatic injury, Zatzick et al. (2010) found that, among individuals presenting with TBIs, including mTBIs, those who screened positive for PTSD had worse self-reported functional health. Among OIF Veterans, Hoge et al. (2008) reported that the associations between mTBI and multiple physical symptoms including chest pain, dizziness, and shortness of breath diminished after accounting for PTSD and depressive symptoms. Similarly, Pietrzak, Johnson, Goldstein, Malley, and Southwick (2009) examined whether PTSD symptoms mediated the relation between screening positive for mTBI on the VA TBI Clinical Reminder (Department of Veterans Affairs, 2007) and self-reported general health in a sample of treatment-seeking OEF/OIF Veterans and found evidence consistent with a mediational model. Partially supporting these findings, Vanderploeg, Belanger, and Curtiss (2009) reported that, in a large-scale sample of Vietnam era U.S. military Veterans, a history of mTBI was associated with multiple self-reported physical health symptoms including fainting, calf pain, and rapid heartbeat. However, the association between mTBI and these physical health symptoms (with the exception of fainting) was largely mitigated by the presence of psychiatric disorders including PTSD and depression. Most recently, Vasterling et al. (2012), in a sample of OIF Veterans assessed as part of the Neurocognition Deployment Health Study, found evidence that a history of deployment-related mTBI was associated with worse self-reported health functioning even after adjusting for PTSD symptoms. So, while these studies seem to yield mixed results, they generally suggest that PTSD symptoms may at least partially, though not fully, explain the association between a history of mTBI and health outcomes.

One shortcoming of this research, however, is that conclusions about the mediational role of PTSD in explaining relations between mTBI and health are based almost entirely on self-reports of physical symptoms and health functioning. Green and Kimerling (2004) commented that negative affect related to traumatic stress may bias self-reports of health in that physical sensations may be inaccurately attributed to medical illness in the absence of any organic pathology and, thus, underscored the importance of corroborating self-reports of symptoms with findings obtained by objective health indices (e.g., physician diagnoses). Another shortcoming of studies suggesting that PTSD mediates the relations between mTBI and health is that mTBI is often treated dichotomously (i.e., screening positive versus screening negative for mTBI). This issue is an important one to address given that individuals may greatly differ in terms of how many postconcussive symptoms they continue to experience long after sustaining an mTBI and raises the question of whether PTSD also mediates the relation between postconcussive symptoms and health outcomes. In other words, more research is needed to determine whether PTSD mediates relations between long-term postconcussive symptoms attributable to brain injury and health.

MTBI, PTSD, and Substance Misuse: Health Implications of Trimorbidity

Any attempt to explore relations between postconcussive symptoms, PTSD, and health outcomes must also take into account the potential adverse effects of substance use behaviors like alcohol and tobacco use. A history of mTBI is common among patients with substance misuse (e.g., Graham & Cardon, 2008), and PTSD commonly co-occurs with both alcohol (e.g., Seal et al., 2011) and tobacco (e.g., Lasser et al., 2000) misuse. Engaging in these substance use behaviors may complicate the health profiles of Veterans with comorbid PTSD and residual postconcussive symptoms, although estimates of substance use rates among Veterans with these comorbid conditions are lacking. Preliminary estimates from one study, however, suggest that as many as 54% of Veterans screening positive for both PTSD and a history of TBI also report being current alcohol users (Graham & Cardon, 2008).

Researchers have extensively studied the negative health consequences of both alcohol and tobacco misuse (Murray & Lopez, 1997). In terms of tobacco use prevalence, one estimate suggested that as many as 53% of Veterans with PTSD may be current smokers (Beckham et al., 1997). When modeled simultaneously with PTSD, studies involving samples of World War II, Korean War, and Vietnam Veterans have consistently found evidence that tobacco use confers additional risk for poor health outcomes (e.g., Beckham et al.; Schnurr & Spiro, 1999). A recent study involving non-treatment-seeking OIF Veterans, however, revealed that, when modeled with PTSD, post-deployment smoking was unrelated to self-reported health complaints (Vasterling et al., 2008). This discrepancy in findings may reflect the longer time lag between heavy tobacco use and the emergence of associated health problems (Murray & Lopez, 1997) in tobacco users given that older Veterans (i.e., World War II, Korean War, and Vietnam Veterans) likely reflect a group with a more chronic pattern of use and, thus, more exposure to the harmful effects of tobacco. It should be noted, though, that none of these studies found evidence that tobacco use mediates relations between PTSD and health outcomes but, rather, that the adverse health effects of co-occurring PTSD and tobacco misuse are cumulative in nature.

While most studies generally yield evidence suggesting that tobacco use contributes to poorer health beyond the effects of PTSD, studies exploring the health effects of alcohol misuse in conjunction with PTSD have yielded very different results. Studies across Veteran samples including OEF/OIF Veterans and Veterans from older cohorts have found no evidence for an association between alcohol use and health after modeling associations with PTSD (e.g., Schnurr & Spiro, 1999; Vasterling et al., 2008). As with smoking, recent evidence among OEF/OIF Veterans also suggests that alcohol use does not mediate relations between PTSD and self-reported health functioning (McDevitt-Murphy et al., 2010). While these results may seem counterintuitive in light of the well-established link between alcohol use and global disease burden (Murray & Lopez, 1997; Room, Babor, & Rehm, 2005), emerging evidence indicates that PTSD may be more strongly related to medical morbidity than substance use disorders, including alcohol-related disorders. For example, Nazarian, Kimerling, and Frayne (2012) found that, among OEF/OIF Veterans, PTSD was associated with increased risk of diagnoses across several major categories of medical conditions whereas substance use disorders increased risk of diagnoses in only 2 major categories of medical conditions, including injuries and poisonings. They further found that there was no statistically significant interaction between PTSD and substance use disorders.

To our knowledge, no studies to date have examined the extent to which tobacco and alcohol use contribute to poorer health above and beyond residual postconcussive symptoms and PTSD among individuals with a history of TBI. Several recent studies do seem to suggest, though, that a history of deployment-related mTBI may increase risk for substance misuse, although the developmental trajectory of substance misuse following TBI does not, for a majority of individuals, appear to be linear. That is, substance use may decline in the immediate post-injury period and begin to increase 2-3 years post-injury (see Najavits, Highley, Dolan, & Fee, 2012, for discussion).

For some Veterans, this pattern of increased substance misuse may evolve into a formal substance use disorder. Carlson et al. (2010) reported that OEF/OIF Veterans screening positive for mTBI evidenced higher rates of substance use disorders than Veterans screening negative for mTBI. Even though a history of mTBI may confer additional risk for alcohol misuse, recent evidence suggests that, at least among heavy drinking Veterans, a history of mTBI is not necessarily associated with a riskier *pattern* of alcohol use compared to the drinking patterns of Veterans without a history of mTBI (Williams, McDevitt-Murphy, Murphy, & Crouse, 2012). Nevertheless, more research is clearly needed to determine whether the increased risk of substance misuse (including tobacco and alcohol use) also increases risk for poor health outcomes among Veterans with a history of mTBI and active postconcussive and PTSD symptoms.

Postconcussive Symptoms: Traumatic Stress By Another Name?

Interpreting relations between postconcussive symptoms, PTSD, and health outcomes may be difficult given the high degree of overlap between PTSD and postconcussive symptoms (Stein & McAllister, 2009), specifically disturbed sleep, irritability, difficulty concentrating, fatigue, and hyperarousal. Furthermore, both PTSD and postconcussive symptoms can theoretically result from the same kinds of incidents (e.g., exposure to blasts, motor vehicle accidents), meaning that, developmentally, these symptoms can have similar onset and course, making their differentiation a formidable task. PTSD is one of the strongest predictors of persistent postconcussive symptoms among OEF/OIF Veterans (Schneiderman, Braver, & Kang, 2008), although PTSD may be more strongly related to some postconcussive symptoms than others. Using the Neurobehavioral Symptom Inventory (NSI) in a sample of recently returned Veterans, Benge, Pastorek, and Thornton (2009) examined the amount of shared variance between each item on the NSI and a measure of PTSD severity. Their findings indicated that as much as 43% of variance in individual items on the NSI (each item corresponds to a unique postconcussive symptom) was explained by PTSD. Affective postconsussive symptoms (e.g., feeling anxious, feeling depressed or sad, irritability) shared the most variance with PTSD while somatic/sensory symptoms including headaches, vision problems, sensitivity to light, and hearing difficulty shared the least amount of variance (6%-8%) with PTSD. Consistent with these findings, Vanderploeg and associates (2009) reported that, after controlling for psychiatric conditions including PTSD and depression, only somatic postconcussive symptoms were associated with a history of mTBI, suggesting that cognitive and affective postconcussive symptoms may share a considerable amount of variance with various psychiatric complaints.

In a sample of OIF troops returning from a 1-year deployment in Iraq, Brenner et al. (2010) found that screening positive for either mTBI alone, PTSD alone, or both in combination was associated with higher rates of postconcussive symptoms than screening negative for both conditions, although screening positive for both conditions was more strongly associated with the prevalence of postconcussive symptoms than screening positive for either condition alone. One limitation of the Brenner et al. study, however, is that it is unclear whether the Veterans in the combined mTBI/PTSD group represent individuals with both physical and psychological injuries or instead a more clinically severe subset of Veterans, perhaps by virtue of more severe PTSD symptoms. Taken together, an implication of this research, then, is that PTSD may mediate relations between postconcussive symptoms and health by virtue of the high degree of overlap between PTSD and postconcussive symptoms.

There are, however, other potential mechanisms by which PTSD may mediate relations between postconcussive symptoms and health. As previously discussed, postconcussive symptoms may heighten vulnerability to trauma-related sequelae like PTSD and PTSD-related health consequences. Thus, as more time passes after a head injury, persistent postconcussive symptoms may increase risk for PTSD, which may then play an important role in health outcomes. The type of health outcome considered may also influence whether PTSD mediates relations between postconcussive symptoms and health. For example, health outcomes like objective measures of neurological disorders might be more strongly related to postconcussive symptoms than PTSD, and, thus, less likely to be mediated by PTSD.

Overall, the emerging literature on the long-term effects of mTBI and PTSD on OEF/OIF Veterans' health suggests that PTSD may at least partially mediate relations between mTBI and poor health, although little research has examined whether such a model is supported with objective indices of health (e.g., morbidity as evidenced by physician-diagnosed conditions) as opposed to self-reported health. Moreover, few studies have attempted to disentangle mTBI-related postconcussive symptoms and PTSD symptoms when exploring the relative contributions of each symptom constellation to post-deployment health outcomes. These unanswered questions are important from both a treatment and public health perspective. If, after accounting for PTSD, postconcussive symptoms uniquely influence disease burden, clinicians may need to direct increased efforts towards treating postconcussive symptoms. If, however, PTSD mediates relations between postconcussive symptoms and disease burden, misattributing greater disease burden to postconcussive symptoms could interfere with clinicians' efforts to provide timely assessment and treatment for PTSD, which may have the secondary benefit of improving postconcussive symptoms and disease burden.

In light of these important theoretical and clinical questions, the proposed study aimed to contribute to the literature on mTBI, PTSD, and health by examining whether PTSD mediates relations between postconcussive symptoms and health using two indices of medical disease burden, system disease burden and cumulative disease burden (Possemato et al., 2010), and a self-report measure of health functioning (Medical Outcomes Study Short-Form 36 Health Survey; Ware & Sherbourne, 1992) for comparison, in a sample of OEF/OIF Veterans seeking VA health care. An advantage of using both disease burden and self-report indices is that this approach provides multiple measures of health that may help corroborate any associations that emerge between postconcussive symptoms, PTSD, and health. Another aim of the proposed study was to examine whether these mediational models could be replicated after removing nonspecific postconcussive and PTSD symptoms.

Research Questions

Research Question 1

The first aim of this study was to explore associations between postconcussive symptoms, PTSD symptoms, and health outcomes. Specific hypotheses were as follows:

Hypothesis 1a: We expected statistically significant, positive relations between both postconcussive and PTSD symptoms and system disease burden, or the number of *ICD-9-CM* major medical categories positive for a diagnosis (except for three categories including conditions originating in the perinatal period, congenital anomalies, and complications of pregnancy or childhood).

Hypothesis 1b: We expected statistically significant, positive relations between postconcussive symptoms, PTSD symptoms, and cumulative disease burden, or the total number of *ICD-9-CM* diagnostic codes listed in a Veteran's records (not including mental health codes, conditions originating in the perinatal period, congenital anomalies, or complications of pregnancy or childhood).

Hypothesis 1c: We expected a statistically significant negative relation between postconcussive symptoms and a composite measure of physical health functioning derived from a self-report measure of health functioning. We also expected a statistically significant negative relation between PTSD and the self-report measure of physical health functioning.

Hypothesis 1d: Statistically significant, positive relations were expected to emerge between both postconcussive and PTSD symptoms and alcohol use severity. Furthermore, we expected statistically significant, positive relations between both postconcussive and PTSD symptoms and tobacco use. Statistically significant, positive relations were expected between substance use behaviors, including alcohol and tobacco use, and both measures of disease burden. Statistically significant, negative relations were expected between both substance use behaviors and a measure of self-reported health functioning.

Research Question 2

Given previous research suggesting that PTSD may partially mediate relations between mTBI and health outcomes (e.g., Hoge et al., 2008; Pietrzak et al., 2009), the second aim of this study was to explore whether PTSD mediated associations between postconcussive symptoms and indices of disease burden. Specific hypotheses were as follows:

Hypothesis 2a: We expected that PTSD symptoms would partially mediate relations between postconcussive symptoms and both disease burden outcomes. A pattern of partial versus full mediation could support the theory that, while postconcussive symptoms related to head injury influence health, they also increase risk for PTSD, which increases disease burden. A pattern of full mediation, however, could indicate that the impact of postconcussive symptoms on disease burden is better explained by the impact of PTSD. On the other hand, a pattern of full mediation could also suggest that the large amount of symptom overlap between PTSD and postconcussive symptoms obscures relations between the long-term consequences of brain injury and health.

<u>Hypothesis 2b:</u> In order to more fully test the theory that postconcussive symptoms increase risk for PTSD, which, in turn, increases disease burden, a series of reverse mediational analyses were conducted to explore whether postconcussive symptoms mediate relations between PTSD and disease burden. We anticipated that postconcussive symptoms would partially mediate relations between PTSD and disease burden, supporting Hypothesis 2a that PTSD symptoms account for a unique proportion of variance in health outcomes among individuals with persistent, postconcussive symptoms. A pattern of results where postconcussive symptoms do not mediate relations between PTSD symptoms and health outcomes would suggest that health complaints among individuals with persistent, postconcussive symptoms are largely associated with PTSD. However, a pattern of results whereby postconcussive symptoms fully mediated relations between PTSD and health outcomes might suggest that PTSD contributes to the chronicity of postconcussive symptoms, which are uniquely and strongly associated with post-deployment health complaints above and beyond the effects of PTSD.

Hypothesis 2c: Additional, exploratory analyses investigated, using the original model where PTSD mediated relations between postconcussive symptoms and health outcomes, whether this pattern of mediation is specific to certain categories of medical conditions. For example, PTSD may only partially mediate relations between postconcussive symptoms and neurological conditions while fully mediating relations between postconcussive symptoms and circulatory system conditions. So, we examined whether PTSD mediated relations between postconcussive symptoms and several categories of medical conditions including infectious diseases, neoplasms, immunity diseases, diseases of the blood, and injuries and poisonings as well as muscuoloskeletal, neurological, digestive, respiratory, skin, circulatory, genitourinary, and idiopathic conditions. Along with specific categories of medical conditions, we conducted exploratory analyses examining whether PTSD mediated relations between postconcussive symptoms and alcohol misuse and tobacco use.

Hypothesis 2d: PTSD was expected to partially mediate relations between postconcussive symptoms and a composite measure of self-reported physical health functioning. Such a pattern of partial mediation would lend additional support to the theory that postconcussive symptoms increase risk for PTSD, and, thus, worse overall health. On the other hand, if the pattern of mediation using self-reported health as the dependent variable was different from the pattern of mediation found using indices of disease burden as the primary outcomes, then the results would suggest that postconcussive symptoms and PTSD do not impact *actual* health in the same way as *perceived* health.

Hypothesis 2e: Hypothesis 2e was exploratory in nature. In order to explore whether mediational models tested in this section are *conditional*, or vary as a function of characteristics associated with mTBI, each model in this section was also tested using a moderated mediation approach (Preacher, Rucker, & Hayes, 2007) where injury characteristics were treated as moderating variables. Given previous literature suggesting that mTBI is associated with adverse health outcomes, especially when loss of consciousness occurs at the time of the injury (e.g., Hoge et al., 2008; Ishibe, Wlordarczyk, & Fulco, 2009), we explored whether each mediational model differed as a function of losing consciousness at the time of the injury. In addition, we explored whether each mediational model differed as a function of the number of probable mTBIs sustained during deployment.

Research Question 3

The high degree of overlap between postconcussive and PTSD symptoms presents a unique challenge in terms of understanding whether PTSD mediates relations between postconcussive symptoms and disease burden. The third aim of this study was to explore whether the results of mediational models tested as part of Research Question 2 could be replicated after removing nonspecific symptoms from the computation of our postconcussive and PTSD symptom variables. In other words, we computed postconcussive and PTSD symptom severity scores using only those symptoms that were most *unique* to each syndrome and conducted a second set of mediational analyses using these new scores. Principal axis factoring was used to determine which symptoms were most unique to each syndrome. Specific hypotheses were as follows:

Hypothesis 3a: We expected that somatic/sensory symptoms (e.g., headache, sensitivity to bright light) would most uniquely represent postconcussive symptoms, while reexperiencing symptoms (e.g., intrusive memories of traumatic events, nightmares) would be most unique to PTSD.

Hypothesis 3b: We anticipated that, after removing nonspecific symptoms from our models, PTSD would continue to partially mediate relations between postconcussive symptoms and disease burden, supporting the theory that PTSD partially accounts for relations between postconcussive symptoms and health outcomes. Furthermore, a pattern of partial mediation where somatic/sensory symptoms most uniquely reflect postconcussive symptoms and reexperiencing symptoms are most unique to PTSD would support the theory that neurological injury resulting from mTBI reduces cognitive capacity to process trauma-memories (Bryant, 2008), increasing risk for PTSD and PTSD-related health problems.

Hypothesis 3c: PTSD was expected to mediate relations between postconcussive symptoms and self-reported physical health functioning after removing nonspecific symptoms from the postconcussive and PTSD severity scores.

Research Question 4

After conducting exploratory analyses to examine whether PTSD mediated relations between postconcussive symptoms and substance use behaviors like alcohol misuse and tobacco use (see Hypothesis 2c), the fourth aim of the study was to examine structural relations between postconcussive and PTSD symptoms, substance use behaviors, and health outcomes (i.e., indices of disease burden and a self-report measure of physical health functioning). Specific hypotheses were:

Hypothesis 4a: The anticipated final multivariate model was expected to reveal a pattern of relations such that PTSD partially mediated relations between postconcussive symptoms and all health indices. Direct relations were also expected between both postconcussive symptoms and PTSD and alcohol misuse and tobacco use. However, consistent with research among other samples of OIF Veterans (e.g., Vasterling et al., 2008), substance use behaviors were not expected to mediate relations between postconcussive symptoms and health outcomes or relations between PTSD and health outcomes.

Chapter 2

Methodology

Sample

Participants for the current study were recruited through the screening phase of an alcohol intervention study. The sample consists of 573 OEF/OIF Veterans recruited through the Memphis VAMC. Descriptively, the sample was predominantly male (n = 522, 91.1%) and ranged in age from 19 to 61 years (M = 34.16, SD = 9.76). A majority of the sample was Caucasian (n = 347, 60.6%) or African American (n = 202, 35.3%). Four individuals did not provide information regarding their racial background. Over half of the sample reported being married (n = 305, 53.2%), and 3 Veterans did not report their marital status.

Data Collection and Instrumentation

Participants were recruited through a Memphis VAMC OEF/OIF combat clinic that serves as a gateway for Veterans seeking VA health care. For all participants, record reviews were conducted to obtain additional information regarding health status, including mTBI screening results and medical diagnoses. Records for all Veterans screening positive for mTBI on the VA TBI Clinical Reminder were also reviewed for any follow-up mTBI evaluations in a Polytrauma clinic. Polytrauma clinic evaluations in the VA typically include multiple assessments for mTBI-related events and postconcussive symptoms, including the NSI, and NSI scores were collected for the current study. On the basis of prevalence estimates suggesting that between 15% to 19% of OEF/OIF Veterans experienced mTBI during deployment (Hoge et al., 2008; Tanielian & Jaycox, 2008), we anticipated that between 88 and 112 Veterans would screen positive for mTBI and complete Polytrauma clinic evaluations. To assess the accuracy of information collected from participants' medical records, 3 trained coders collected a subset of the chart data (records from 60 Veterans, or 10.5% of the full sample). Coders evidenced excellent interrater agreement with less than 1% overall error rate. All data collected from Veterans' medical records were de-identified, and procedures were approved by the University of Memphis and Memphis VAMC Internal Review Boards. Participants provided informed consent prior to completing the screening packet.

Data for the present investigation involve a combination of self-report measures and data from participants' VAMC medical records. Measures include a screening instrument for mTBI, assessments of postconcussive symptoms and PTSD, and health indices, including objective, clinical indices of disease burden and a subjective measure of physical health functioning.

VA TBI Clinical Reminder. The VA TBI Clinical Reminder is a brief, 4-part screen for mTBI administered to all OEF/OIF Veterans seeking VA health care (Department of Veterans Affairs, 2007). The screener consists of an initial prompt question asking whether the Veteran received a TBI diagnosis during an OEF or OIF deployment, and an affirmative response on this initial question yields a positive screen. Veterans with a negative response on the prompt question complete a series of additional questions organized into 4 sections assessing exposure to mTBI-related events, symptoms in the immediate aftermath of the event, symptoms following the event, and current symptoms. Unlike some screening measures, the VA TBI Clinical Reminder does not yield a severity score, per se, but, rather, classifies individuals as either positive or negative for a history of probable mTBI. A positive screen requires an affirmative response to at least one item in each section, and Veterans with a positive screen are subsequently referred to a Polytrauma clinic for further clinical evaluation. Diagnostic information from participants' Polytrauma evaluations was collected to document whether Veterans screening positive for mTBI also received a confirmed mTBI diagnosis. Additional information about mTBIs sustained during deployment was collected from Veterans' Polytrauma evaluations, specifically whether Veterans lost consciousness at the time of an injury event and the number of probable mTBIs sustained during deployment.

Neurobehavioral Symptom Inventory (NSI). The NSI (Cicerone & Kalmar, 1995) is a 22-item self-report measure of cognitive, affective, and somatic postconcussive symptoms. On each item, respondents rate how much they have been bothered by a particular symptom in the past 2 weeks. Symptoms are rated on a 5-point Likert-type scale ranging from 0 to 4 where a score of 4 is associated with greater symptom severity. Total scores can range from 0 to 88. Although studies using the NSI have generally yielded mixed findings in terms of the NSI's validity (e.g., Benge et al., 2009; Cicerone & Kalmar, 1995), the NSI is widely thought to assess three clusters of postconcussive symptoms, including cognitive, affective, and somatic symptoms (Caplan et al., 2010). The NSI has shown excellent internal consistency reliability in clinical samples of patients with mild brain trauma (Gizzi, Zlotnick, Cicerone, & Riley, 2003) and demonstrated excellent reliability in the current sample (α = .95).

Posttraumatic Stress Disorder Checklist – Military Version (PCL-M). The PCL-M (Weathers, Litz, Herman, Huska, & Keane, 1993) is a 17-item self-report measure corresponding to the *DSM-IV-TR* (APA, 2000) symptom criteria for PTSD. For each item, respondents indicate how much they have been bothered by a particular symptom during the past month using a 5-point Likert-type scale ranging from 1 (*Not at All*) to 5 (*Extremely*). The PCL-M assesses each of the *DSM-IV* symptoms of PTSD including re-experiencing the trauma, avoidance of trauma-related cues, emotional numbing, and hyperarousal. Items can be summed to derive an overall symptom severity score where higher scores are suggestive of more severe symptoms. Total scores on the PCL-M can range from 17 to 85. The PCL-M has shown excellent psychometric properties in samples of OEF/OIF Veterans (Grieger, Kolkow, Spira, & Morse, 2007; Pietrzak et al., 2009), and excellent reliability was observed in the current sample (α = .96).

Disease Burden. Disease burden was assessed using medical diagnoses collected from participants' VAMC medical records. Medical diagnoses were coded using the *International Classification of Diseases* (*ICD-9-CM*; U.S. Department of Health and Human Services, 1991) coding system. All medical conditions diagnosed by a VA clinician within one year following completion of the self-report screening packet were used to derive measures of both system and cumulative disease burden. Accordingly, all conditions were diagnosed following combat deployments. Consistent with Possemato et al.'s (2010) definitions of system and cumulative disease burden, system disease burden was defined as the number of *ICD-9-CM* major medical categories positive for a diagnosis, and cumulative disease burden was defined as the total number of *ICD-9-CM* diagnostic codes (not including mental health codes) listed in a Veteran's records. Conditions categorized in the *ICD-9-CM* as originating in the perinatal period, congenital anomalies, or complications of pregnancy or childhood were not computed as part of either disease burden variable since these conditions would have theoretically originated pre-deployment and would therefore be unrelated to any combat trauma.

Medical Outcomes Study Short Form-36 Health Survey (SF-36). The SF-36 (Ware & Sherbourne, 1992) is a 36-item self-report measure of health functioning and health-related quality of life. Items assess 8 subscales of physical and health functioning, including physical functioning, role limitations due to physical health, role limitations due to emotional problems, vitality, mental health, social functioning, pain, and general health. Items are scored using Likert-type response options, and subscale scores range from 0 to 100 where higher scores are indicative of better functioning. Subscale scores can also be used to derive 2 composite scores, a Physical Component Summary and a Mental Component Summary, each of which are converted to T-scores (M = 50, SD = 10). As with subscale scores, higher scores on the composites are indicative of better functioning. Scales from the SF-36 have shown good internal consistency in samples of OEF/OIF Veterans (e.g., McDevitt-Murphy et al., 2010), and each of the subscales demonstrated good reliability in the current sample (Chronbach's alphas ranged from .79 to .93).

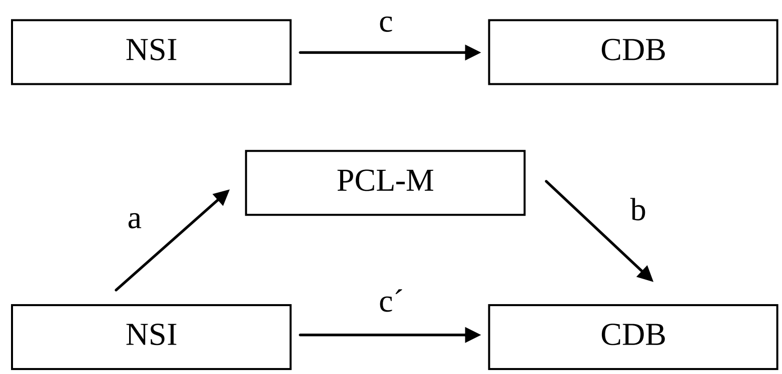
Alcohol Use Disorders Identification Test (AUDIT). The AUDIT (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) is a 10-item self-report measure assessing 3 areas of alcohol use, including consumption, dependence symptoms, and alcohol-related consequences. Items are rated on a Likert-type scale ranging from 0 to 4, and items can be summed to derive an overall alcohol use severity score. Total scores range from 0 to 40 where higher scores are suggestive of more severe alcohol use. A cut-score of 8 is typically used to screen for individuals at risk for alcohol misuse (e.g., Reinert & Allen, 2002). The AUDIT has shown good internal consistency among OEF/OIF Veterans (e.g., McDevitt-Murphy et al., 2010) and similarly demonstrated good reliability in the current sample (α = .87).

VA Tobacco Screen. The VA Tobacco Screen is a brief screening instrument administered to all Veterans seeking healthcare within the VA system, consistent with recommendations from the U.S. Public Health Service (2008). The screen categorizes individuals into 1 of 3 categories, including a category indicating whether Veterans are current smokers or smokeless tobacco users (or quit tobacco less than 12 months prior to the screen). Non-tobacco users are categorized into two groups – a) former smokers or smokeless tobacco users who stopped tobacco use between 1 and 7 years prior to the screen and b) lifetime non-tobacco users or individuals who quit more than 7 years prior to the screen.

Statistical Analysis

With regard to Research Question 1, relations between postconcussive symptoms, PTSD symptoms, health risk behaviors, and health indices were explored using Pearson's correlation statistics. Variables for these analyses included summed scores from the NSI, PCL-M, and AUDIT, a categorical variable indicating Veterans' current tobacco use status, measures of system and cumulative disease burden, and the Physical Component Summary from the SF-36. In regard to Research Question 2, structural relations between postconcussive symptoms, PTSD symptoms, and health indices were assessed using a series of mediational models where PTSD symptoms were modeled as a potential mediator between postconcussive symptoms and disease burden (see Figure 1). A series of mediational models were assessed where PTSD symptoms were modeled as a potential

A



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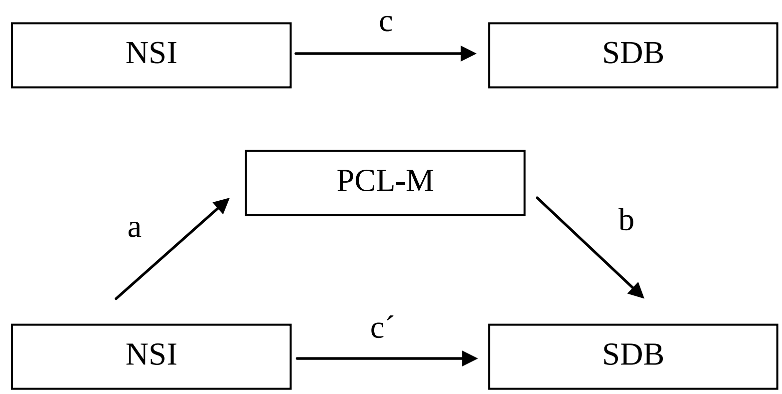

Figure 1. Mediational model for postconcussive symptoms, PTSD, and disease burden.

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; CDB = cumulative disease burden; SDB = system disease burden.

mediator between postconcussive symptoms and each major medical category used to derive the measure of system disease burden. Likewise, PTSD was modeled as a potential mediator between postconcussive symptoms and SF-36 Physical Component Summary scores. Reverse meditational models were assessed where postconcussive symptoms were modeled as a potential mediator between PTSD symptoms and each health outcome (see Figure 2). Mediation was tested using bootstrapping procedures (Preacher & Hayes, 2008), which model the indirect effects of independent variables on dependent variables

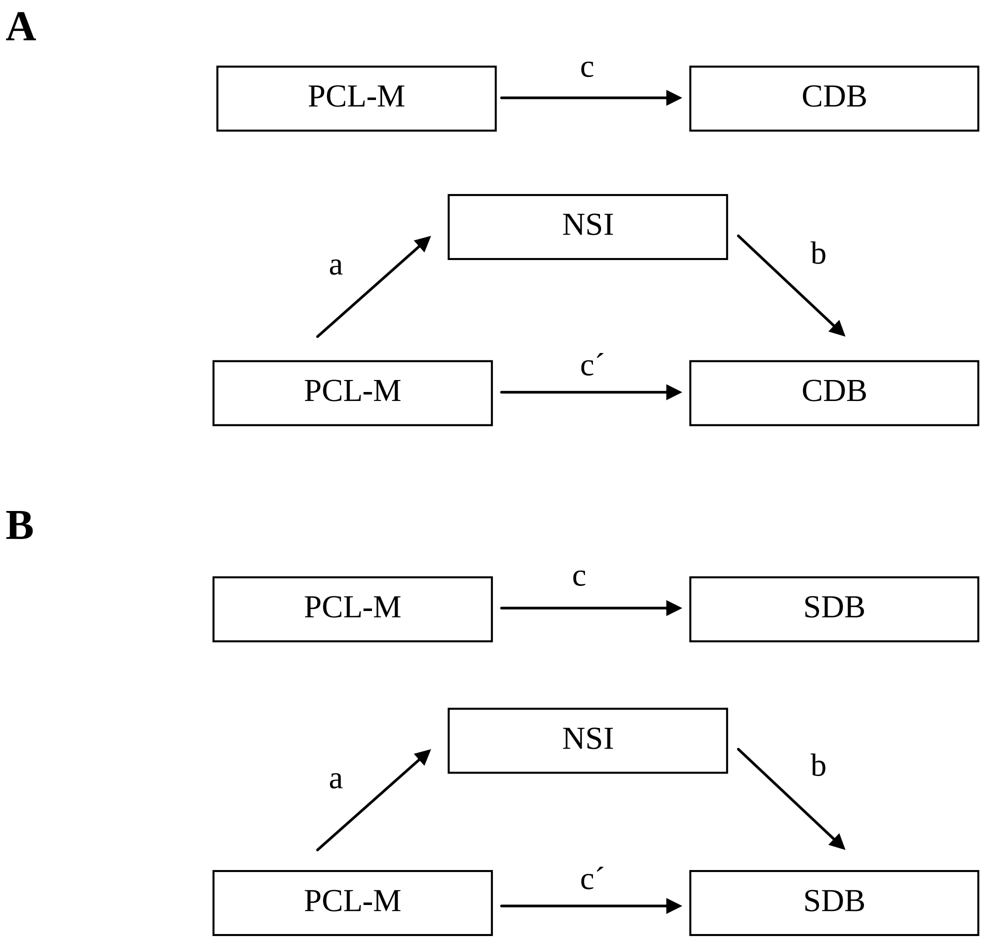

Figure 2. Reverse mediational model for postconcussive symptoms, PTSD, and disease burden.

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; CDB = cumulative disease burden; SDB = system disease burden.

after controlling for the effects of any potential mediators. An advantage of bootstrapping is that indirect effects are estimated using random samples from a dataset such that all data points are equally likely to be selected with each random sample. Consequently, large numbers of random samples may be drawn from the same dataset, and these random samples can then be used to model the distribution of a specified population parameter (Mallinckrodt, Abraham, Wei, & Russell, 2006). Bootstrapping procedures were also used to conduct moderated mediation analyses where loss of consciousness following an mTBI and the number of probable mTBIs sustained during deployment (as documented in Veterans' Polytrauma evaluations) were modeled as potential moderators in each of the mediational models tested.

Research Question 3 exploring symptoms most uniquely representative of postconcussive and PTSD symptomatology was conducted using principal axis factoring. Principal axis factoring is well suited to determining whether a particular set of variables are distinct from another set of variables since error and variance unique to each variable are omitted from the analysis (Tabachnick & Fidell, 2007). That is, principal axis factoring utilizes shared variance between observed variables to determine which variables cluster together into discrete factors. While principal axis factoring generally produces more reliable estimates with larger sample sizes, some researchers have suggested that factor analyses can produce reliable solutions with samples as small as 50 cases (Sapnas & Zeller, 2002). After identifying symptoms most uniquely representative of postconcussive and PTSD symptoms, new symptom severity scores were derived for both variables by summing the items most representative of each construct. These variables were then used in a second set of mediational analyses (using bootstrapping procedures) to explore whether PTSD mediates relations between postconcussive symptoms and each health measure after removing non-unique symptoms from the analyses.

Research Question 4 examining structural relations between postconcussive and PTSD symptoms, substance use behaviors, and health outcomes was tested using path analysis. The expected, final structural model is depicted in Figure 3. The path analysis was conducted using Mplus Version 3.1 software (Muthèn & Muthèn, 1998-2004). The

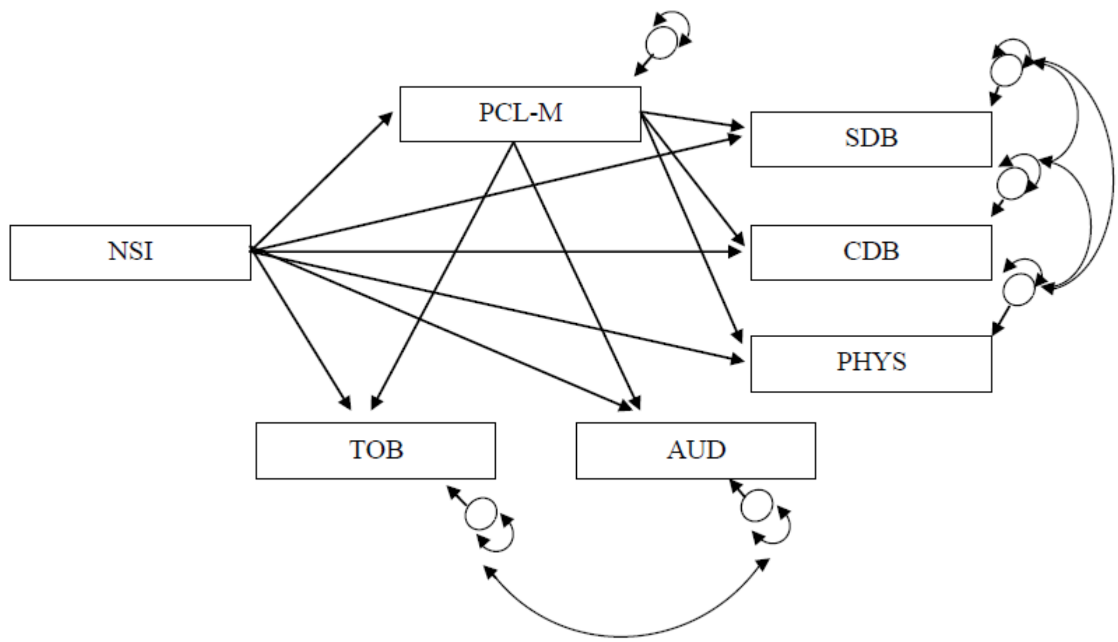

Figure 3. Expected final, multivariate model.

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; AUD = Alcohol Use Disorders Identification Test; TOB = VA Tobacco Screen; SDB = system disease burden; CDB = cumulative disease burden; PHYS = SF-36 Physical Component Summary.

weighted least squares estimator was used for model estimation given that this estimator can accommodate models involving categorical variables (e.g., tobacco use).

Chapter 3

Results

Descriptive Statistics

Participants reported having served a mean of 1.48 (*SD* = .74) OEF/OIF combat deployments, although 24 Veterans did not indicate how many times they were deployed. Veterans reported spending an average of 14.19 months (*SD* = 8.60) in a combat zone, but this information was not available for 12 Veterans. In terms of mTBI, 550 (96.0%) Veterans received documented mTBI screens, and, of those Veterans with documented screens, 120 (21.8%) Veterans screened positive for mTBI. The frequency of endorsement for each item on the mTBI screener is reported in Table 2.

Table 2

Frequency of Item Endorsement on the VA TBI Clinical Reminder among 120 Veterans Screening Positive for mTBI

	Yes *n* (%)	No *n* (%)
Have you ever been diagnosed as having TBI during OEF/OIF deployment?	17 (14.2%)	103 (85.8%)
Section 1: Did you experience any of the following during OEF/OIF?[a]		
Blast or explosion (e.g., IED, RPG, land mine)	82 (79.6%)	20 (19.4%)
Vehicular accident/crash	48 (46.6%)	54 (52.4%)
Fragment or bullet wound above your shoulders	6 (5.8%)	96 (93.2%)

(*table continues*)

Table 2. (continued)

Frequency of Item Endorsement on the VA TBI Clinical Reminder among 120 Veterans Screening Positive for mTBI

	Yes *n* (%)	No *n* (%)
Fall	46 (44.7%)	56 (54.4%)
Blow to the head	19 (18.4%)	83 (80.6%)
Other injury to the head	3 (2.9%)	99 (96.1%)
Section 2: Did any of the following happen to you, or were you told happened to you, IMMEDIATELY after any of these events?[a]		
Lost consciousness or got "knocked out"	22 (21.4%)	80 (77.7%)
Feeling dazed, confused, or "saw stars"	88 (85.4%)	14 (13.6%)
Didn't remember the event	23 (22.3%)	79 (76.7%)
Had a concussion	16 (15.5%)	86 (83.5%)
Had a head injury	20 (19.4%)	82 (79.6%)
Section 3: Did any of the following problems begin or get worse after these events?[a]		
Memory problems or lapses	59 (57.3%)	43 (41.7%)
Balance problems or dizziness	41 (39.8%)	61 (59.2%)
Sensitivity to bright light	41 (39.8%)	61 (59.2%)
Irritability	59 (57.3%)	43 (41.7%)
Headaches	68 (66.0%)	34 (33.0%)

(*table continues*)

Table 2. (continued)

Frequency of Item Endorsement on the VA TBI Clinical Reminder among 120 Veterans Screening Positive for mTBI

	Yes *n* (%)	No *n* (%)
Sleep problems	77 (74.8%)	25 (24.3%)
Section 4: In the past week, have you had any of these symptoms?		
Memory problems or lapses	55 (53.4%)	48 (46.6%)
Balance problems or dizziness	34 (33.0%)	69 (67.0%)
Sensitivity to bright light	39 (37.9%)	64 (62.1%)
Irritability	62 (60.2%)	41 (39.8%)
Headaches	64 (62.1%)	39 (37.9%)
Sleep problems	82 (79.6%)	21 (20.4%)

Note. Item responses in sections 1 through 4 were not recorded in the medical records of Veterans responding "yes" to the initial prompt question, "Have you ever been diagnosed as having TBI during OEF/OIF deployment?" Rates of endorsement for items in sections 1 through 4 are based on the responses of 103 Veterans who screened positive for mTBI but answered "no" on this initial prompt question.
[a]Responses to items in this section were missing for 1 Veteran.

The mean PCL-M score for the full sample was 38.52 (*SD* = 17.66), although PCL-M scores were not available for 7 Veterans. Among Veterans with valid PCL-M scores, 156 (27.6%) screened positive for PTSD, using a cut score of 50. In terms of substance use behaviors, the mean AUDIT score for the full sample was 4.94 (*SD* = 6.06), although AUDIT scores were not available for 6 Veterans. Among those Veterans with valid AUDIT scores, 123 (21.7%) Veterans screened positive for heavy drinking based on a score of 8 or higher. Five hundred-forty Veterans received documented tobacco use screens as recorded in their VA medical records, and, of these Veterans, 287 (53.1%) reported never using tobacco or having quit tobacco use more than 7 years prior to the screen, 22 (4.1%) reported quitting tobacco use between 1 and 7 years prior to the screen, and 231 (42.8%) reported currently using tobacco or having quit within one year prior to the screen.

Regarding health in the overall sample, medical records were available for 560 Veterans. The mean number of clinician-diagnosed conditions (excluding mental health and TBI-related diagnoses, conditions originating in the perinatal period, congenital anomalies, and complications of pregnancy or childhood) in Veterans' VA medical records, or cumulative disease burden, was 3.23 (*SD* = 2.44). The mean number of major medical categories positive for at least one-diagnosed condition (excluding categories including mental health conditions, conditions originating in the perinatal period, congenital anomalies, and complications of pregnancy or childhood), or system disease burden, was 2.36 (*SD* = 1.56). On the SF-36, the mean Physical Component Summary (PCS) score (a self-report indicator of overall physical health functioning) was 44.25 (*SD* = 11.02), suggesting slightly below average physical health functioning compared to general population-based norms. PCS scores were not available for 37 Veterans.

Ninety-five (79.2%) Veterans who screened positive for mTBI completed full Polytrauma evaluations for TBI. Two more Veterans who did not initially screen positive for mTBI were eventually referred for and completed Polytrauma evaluations, resulting in a total of 97 Veterans completing Polytrauma evaluations. This subset of Veterans represents 16.9% of the overall sample. Information coded for the current study was unavailable in the Polytrauma evaluations of 2 Veterans, and 5 Veterans' Polytrauma results were not included in the current study because their evaluations occurred more than 3 months prior to or 3 months after completing the screening measures. Consequently, their scores on measures of postconcussive symptoms may not reflect their symptoms at the time of completing the screening packet. As a result, valid Polytrauma results, including item scores on the Neurobehavioral Symptom Inventory (NSI; Cicerone & Kalmar, 1995), were available for 91 Veterans. The average length of time between completing the screening packet at the OEF/OIF combat clinic and completing Polytrauma evaluations for TBI was approximately 3 weeks (*M* = 22.12 days, *SD* = 19.09). Data collected with the Polytrauma evaluations suggest that the majority of Veterans (*n* = 82, 90.1%) screening positive for mTBI sustained at most mild injuries using the definition of mTBI as an injury involving less than 30 minutes loss of consciousness and no more than 24 hours of posttraumatic amnesia (Alexander, 1995; Hoge et al., 2009). Since data for these 91 Veterans will be used in all subsequent analyses, variables were examined for outliers and possible violations of the assumption of univariate normality. The only severely skewed and kurtotic variable was the total AUDIT score, which was corrected using a square-root transformation.

Of the 91 Veterans who completed Polytrauma evaluations, the majority was male (*n* = 86, 94.5%), and the mean age was 32.71 (*SD* = 7.94). As with the full sample, the majority was Caucasian (*n* = 54, 59.3%) or African American (*n* = 32, 35.2%). Nearly half of these Veterans reported being married (*n* = 44, 48.4%) and one Veteran did not report his marital status.

The mean NSI total score for this subset of 91 Veterans was 36.46 (*SD* = 17.86). The mean PCL-M score for this subset of Veterans was 54.09 (*SD* = 16.45), although 2 Veterans did not complete the PCL-M, resulting in valid data for 89 of the 91 Veterans. Fifty-four (60.7%) Veterans completing the PCL-M screened positive for PTSD using a cut score of 50. Similarly, 2 Veterans did not complete the AUDIT, resulting in valid data for 89 of the 91 Veterans. On the AUDIT, scores for 2 Veterans were identified as outliers since their scores were more than 3.29 standard deviations above the mean. Their scores were corrected by changing them to a value within one unit of the greatest non-outlier value. After correcting outliers on the AUDIT, the mean AUDIT score for Veterans completing Polytrauma evaluations was 6.43 (*SD* = 6.98). Twenty-seven (30.3%) Veterans completing the AUDIT scored above the threshold of 8, which is widely used to identify individuals at risk for alcohol misuse. Forty-two (46.2%) of these Veterans reported never using tobacco or having quit tobacco use more than 7 years prior to being screened for tobacco use, 1 (1.1%) reported quitting tobacco use between 1 and 7 years prior to the screen, and 48 (52.7%) reported currently using tobacco or having quit within one year prior to the screen.

On health outcome variables, Veterans completing Polytrauma evaluations received on average 5.14 (*SD* = 2.65) clinician-diagnosed medical conditions (the measure of cumulative disease burden) over the course of 1 year after completing the screening packet. These diagnoses spanned, on average, 3.14 (*SD* = 1.40) categories of medical conditions (the measure of system disease burden). The mean SF-36 Physical Component Summary (PCS) score for Veterans completing Polytrauma evaluations was

38.63 (*SD* = 10.98), although PCS scores were unavailable for 9 Veterans due to incomplete or missing data.

Bivariate Correlations Between Variables

Prior to testing mediational models, relations between variables were explored using Pearson correlation statistics. Relations were also explored between demographic variables and the primary variables of interest (i.e., NSI and PCL-M total scores, substance use behavior variables, and health outcome variables), given that demographic variables including gender, age, and marital status are often associated with measures of mental and physical health (e.g., Possemato et al., 2010). Results are presented in Table 3.

Hypothesis 1a. A medium correlation was found between NSI scores and system disease burden ($r = .32$, $p < .01$). Contrary to our hypothesis, the association between PCL-M scores and system disease burden was not statistically significant. No demographic variables (i.e., gender, age, marital status) were associated with system disease burden.

Hypothesis 1b. As predicted, a large correlation was found between NSI scores and cumulative disease burden ($r = .53$, $p < .01$). Moreover, a statistically significant correlation was found between PCL-M scores and cumulative disease burden ($r = .32$, $p < .01$). No demographic variables were associated with cumulative disease burden.

Hypothesis 1c. Consistent with our hypotheses, a statistically significant, negative correlation emerged between NSI scores and SF-36 PCS scores ($r = -.39$, $p < .01$). No statistically significant correlation was observed between PCL-M and PCS scores. In terms of relations with demographic factors, age was negatively correlated with

Table 3

Bivariate Correlations between Postconcussive Symptom, PTSD, Health, and Demographic Variables

Variables	1	2	3	4	5	6	7	8	9	10
1. NSI	--	.74**[b]	.16[b]	.05	.53**	.32**	-.39**[d]	-.08	.13	.09[a]
2. PCL-M		--	.42**[c]	.00[b]	.32**[b]	.07[b]	-.16[e]	-.10[b]	.07[b]	.02[c]
3. AUDIT			--	.11[b]	-.02[b]	-.01[b]	.15[e]	-.19†[b]	-.14[b]	-.22*[c]
4. TOB				--	.00	.01	-.12[d]	.04	-.26*	.22[a]
5. CDB					--	.78**	-.35**[d]	.06	.04	.17[a]
6. SDB						--	-.24*[d]	.15	.00	.15[a]
7. PHYS							--	-.08[d]	-.22*[d]	-.09[e]
8. Gender								--	-.02	-.04[a]
9. Age									--	.06[a]
10. MAR										--

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; AUDIT = Alcohol Use Disorders Identification Test; TOB = VA Tobacco Screen; CDB = Cumulative Disease Burden; SDB = System Disease Burden; PHYS = SF-36 Physical Component Summary; MAR = Marital Status. AUDIT scores in these analyses were transformed using square-root transformations. Phi coefficients are reported when examining the association between two categorical variables.
[a]$n = 90$. [b]$n = 89$. [c]$n = 88$. [d]$n = 82$. [e]$n = 81$. † $p < .10$. *$p < .05$. **$p < .01$.

PCS scores ($r = -.22$, $p < .05$) such that older age was associated with worse self-reported health functioning.

Hypothesis 1d. A large, statistically significant correlation emerged between NSI and PCL-M total scores ($r = .74$, $p < .01$). A statistically significant correlation also emerged between total AUDIT scores and PCL-M scores ($r = .42$, $p < .01$); however, contrary to our hypotheses, no statistically significant relations emerged between AUDIT scores and NSI scores. Also contrary to our hypotheses, neither NSI nor PCL-M scores were associated with tobacco use. No demographic variables were associated with NSI or PCL-M scores.

Mediation Analyses Using Bootstrap Resampling Methods

Hypothesis 2a. A series of regression analyses with bootstrap estimates of indirect effects were conducted to explore whether PCL-M scores mediated relations between NSI scores and health outcomes. Results are presented in Table 4. A statistically significant, direct effect was found between NSI scores and cumulative disease burden, and PCL-M scores did not appear to mediate this association. Mediation analyses were not conducted with system disease burden as a dependent variable because PCL-M scores were not associated this variable. Therefore, the basic conditions for mediation were not satisfied.

Hypothesis 2b. A series of reverse mediational analyses were conducted to explore whether NSI scores mediate associations between PCL-M scores and cumulative disease burden. Results are presented in Table 5. A direct effect was found between NSI scores and cumulative disease burden although no direct effect was found between PCL-M scores and cumulative disease burden after modeling associations with NSI scores.

Table 4

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Health Outcomes

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Cumulative Disease Burden (n = 89)			.30			
c (NSI → CDB)	.08**	.01				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → CDB)	-.03	.02				
c´	.10**	.02				
a x b				-.02	.01	-.05, .01

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; CDB = Cumulative Disease Burden.
[†] $p < .10$. *$p < .05$. **$p < .01$.

The total effect for PCL-M scores on cumulative disease burden was statistically significant, though, and bootstrap confidence intervals of the indirect effect suggested that NSI scores mediated relations between PCL-M scores and cumulative disease burden.

Hypothesis 2c. To explore whether the pattern of results obtained in our primary analyses are specific to certain categories of medical conditions, a series of regression analyses with bootstrap estimates of indirect effects were conducted to explore whether PCL-M scores mediated relations between NSI scores and each *ICD-9-CM* major

Table 5

Regression Analyses with Bootstrap Estimates: Postconcussive Symptoms Mediating Relations between PTSD and Health Outcomes

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Cumulative Disease Burden (n = 89)			.30			
c (PCL-M → CDB)	.05**	.02				
a (PCL-M → NSI)	.80**	.08				
b (NSI → CDB)	.10**	.02				
c´	-.03	.02				
a x b				.08	.02	.04, .13

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; CDB = Cumulative Disease Burden.
† $p < .10$. *$p < .05$. **$p < .01$.

medical category. Frequencies for diagnostic conditions within each *ICD-9-CM* major medial category are presented in Table 6. The most commonly diagnosed conditions among Veterans in the Polytrauma sample included mental disorders, nervous system and sense organ disorders, musculoskeletal diseases, and idiopathic complaints.

The results of mediational analyses with *ICD-9-CM* major medical categories included as dependent variables are presented in Table 7. For these analyses, the number of conditions within each category was calculated at the individual level to derive

Table 6

Frequencies of ICD-9-CM Medical Conditions among 91 Veterans with Valid Polytrauma Evaluations

Conditions (*ICD-9-CM* Codes)	Frequency (%)
Infectious and Parasitic Diseases (001 - 139)	3 (0.5%)
Neoplasms (140 - 239)	1 (0.2%)
Endocrine, Nutritional, and Metabolic Diseases and Immunity Disorders (240 - 279)	17 (2.7%)
Diseases of the Blood and Blood-Forming Organs (280 - 289)	2 (0.3%)
Mental Disorders (290 - 319)	128 (20.1%)
Diseases of the Nervous System and Sense Organs (320 - 389)	77 (12.1%)
Diseases of the Circulatory System (390-459)	17 (2.7%)
Diseases of the Respiratory System (460 - 519)	16 (2.5%)
Diseases of the Digestive System (520 - 579)	28 (4.4%)
Diseases of the Genitourinary System (580 - 629)	5 (0.8%)
Complications of Pregnancy, Childbirth, and the Puerperium (630 - 677)	--
Diseases of the Skin and Subcutaneous Tissue (680 - 709)	9 (1.4%)
Diseases of the Musculoskeletal System and Connective Tissue (710 - 739)	140 (22.0%)
Congenital Anomalies (740 - 759)	40 (6.3%)
Certain Conditions Originating in the Perinatal Period (760 – 779)	1 (0.2%)
Symptoms, Signs, and Ill-Defined Conditions (780 - 799)	145 (22.8%)

(*table continues*)

Table 6. (continued)

Frequencies of ICD-9-CM Medical Conditions among 91 Veterans with Valid Polytrauma Evaluations

Conditions (*ICD-9-CM* Codes)	Frequency (%)
Symptoms, Signs, and Ill-Defined Conditions (780 - 799)	145 (22.8%)
Injury and Poisoning (800 - 999)	8 (1.3%)

continuous measures of disease impact within each category of medical condition. Analyses were not conducted with 6 categories of medical conditions (i.e., infectious diseases, neoplasms, diseases of the blood, genitourinary, skin conditions, injuries and poisonings) given that fewer than 8 Veterans had diagnoses within each of these categories. Furthermore, analyses were not conducted with conditions originating in the perinatal period, congenital anomalies, or complications of pregnancy or childhood since onset of these conditions would be theoretically unrelated to combat trauma and would precede any military service.

After modeling associations with PCL-M scores, NSI scores were independently associated with endocrine, nutritional, and metabolic diseases and immunity disorders, digestive conditions, and idiopathic complaints. No statistically significant direct effect was found between PCL-M scores and any of the major medical categories. So, PCL-M scores did not appear to mediate relations between NSI scores and any major medical category. Since several postconcussive symptoms assessed on the NSI are commonly coded as idiopathic complaints (i.e., dizziness, poor coordination, numbness in parts of the body, changes in taste and smell, headache, and sleep problems), we re-ran analyses examining whether PCL-M scores mediated relations between NSI scores and idiopathic

Table 7

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Endocrine, Nutritional, and Metabolic Diseases and Nutritional Disorders[a]			.10			
c (NSI → ENM)	.00**	.00				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → ENM)	-.00	.00				
c´	.00**	.00				
a x b				-.00	.00	-.00, .00
Diseases of the Nervous System and Sense Organs[b]			.04			
c (NSI → NRV)	.01[†]	.00				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → NRV)	-.01	.01				
c´	.01[†]	.01				
a x b				-.00	.00	-.01, .00

(*table continues*)

Table 7. (continued)

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	*R²*	*B*	*SE*	*95% CI*
Diseases of the Circulatory System[c]						
c (NSI → CIR)	-.00	.02				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → CIR)	-.02	.02				
c´	.01	.02				
a x b				-.02	.02	-.05, .02
Diseases of the Respiratory System[a]			.01			
c (NSI → RES)	-.00	.00				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → RES)	-.00	.00				
c´	.00	.00				
a x b				-.00	.00	-.00, .00
Diseases of the Digestive System[a]			.17			
c (NSI → DIG)	.00**	.00				

(*table continues*)

Table 7. (continued)

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → DIG)	-.00	.00				
c´	.00**	.00				
a x b				-.00	.00	-.00, .00
Diseases of the Musculoskeletal System and Connective Tissue[b]			.05			
c (NSI → MUSC)	.01*	.00				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → MUSC)	-.00	.01				
c´	.01[†]	.01				
a x b				-.00	.00	-.01, .01
Symptoms, Signs, and Ill-Defined Conditions[b]			.10			
c (NSI → ILL)	.01**	.00				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → ILL)	.00	.01				

(*table continues*)

Table 7. (continued)

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
c´	.01*	.01				
a x b				-.00	.00	-.01, .01
Mental Disorders[b]			.27			
c (NSI → MEN)	.02**	.00				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → MEN)	.00	.01				
c´	.01**	.00				
a x b				.00	.00	-.00, .01

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; ENM = Endocrine, Nutritional, and Metabolic Diseases and Immunity Disorders; NRV = Diseases of the Nervous System and Sense Organs; CIR = Diseases of the Circulatory System; RES = Diseases of the Respiratory System; DIG = Diseases of the Digestive System; MUSC = Diseases of the Musculoskeletal System and Connective Tissue; ILL = Symptoms, Signs, and Ill-Defined Conditions; MEN = Mental Disorders. *N* = 89 for all analyses.
[a]Variable transformed using log transformations.
[b]Variable transformed using square-root transformations.
[c]Given that no Veterans had more than one circulatory system disorder, the dependent variable was binary, and a logistic regression model was used for the analysis. However, R^2 cannot be derived for non-linear models and is unavailable.
† $p < .10$. *$p < .05$. **$p < .01$

complaints after removing shared symptoms from the idiopathic complaints variable. Interestingly, neither NSI nor PCL-M scores were associated with idiopathic complaints after removing commonly endorsed postconcussive symptoms from the variable (see

Table 8). We conducted exploratory analyses investigating whether PCL-M scores mediated relations between NSI scores and mental health diagnoses, and results suggested that NSI scores were independently associated with the number of mental health diagnoses (excluding PTSD and postconcussive syndrome) after modeling associations with PCL-M scores. PCL-M scores were not directly associated with the number of mental health diagnoses and, thus, did not appear to mediate relations between NSI scores and mental health diagnoses.

Table 8

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Idiopathic Complaints after Removing Complaints Shared with the NSI

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Symptoms, Signs, and Ill-Defined Conditions[a] (*n* = 89)			.02			
c (NSI → ILL)	.00	.00				
a (NSI → PCL-M)	.68**	.07				
b (PCL-M → ILL)	-.00	.00				
c´	.00	.00				
a x b				-.00	.00	-.00, .00

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; ILL = Symptoms, Signs, and Ill-Defined Conditions.
[a]Variable transformed using log transformations.
† $p < .10$. *$p < .05$. **$p < .01$.

A mediation analysis was not conducted using AUDIT scores as the dependent variable since the association between NSI scores and AUDIT scores was not statistically significant. Therefore, the basic conditions for mediation were not satisfied. Furthermore, a mediation analysis was not conducted using tobacco use status as a dependent variable given that neither NSI nor PCL-M scores were significantly associated with tobacco use.

Hypothesis 2d. Mediation analyses were not conducted using SF-36 PCS scores as dependent variables since PCL-M scores were not associated PCS scores. Therefore, the basic conditions for mediation were not satisfied.

Hypothesis 2e. To explore whether our primary mediational model was conditional as a function of characteristics associated with the TBI, we conducted a series of moderated mediation analyses with injury characteristics included as moderating variables. Specifically, we explored whether there were moderating effects for losing consciousness following an injury and sustaining multiple injuries. Results are presented in Table 9.

Table 9

Moderated Mediation Analyses as a Function of Losing Consciousness and Sustaining Multiple Injuries: Cumulative Disease Burden

		Conditional Indirect Effect	*SE*	*Z*
Loss of Consciousness[a]	LOC	-.00	.03	-.04
	No LOC	-.02	.02	-1.28
Number of mTBIs[b]	1 mTBI	-.02	.02	-.96
	> 1 mTBI	-.02	.02	-.81

[a]*n* = 89. [b]*n* = 88. † *p* < .10. **p* < .05. ***p* < .01.

More than one-third of Veterans completing Polytrauma evaluations reported losing consciousness for at least one minute or less following an injury (*n* = 32, 35.2%), and over half of the sample reported multiple injury events (*n* = 58, 63.7%). There was no conditional mediation of NSI scores on cumulative disease burden via PCL-M scores as a function of either losing consciousness at the time of the injury (*bootstrap 95% CI* = -.08, .05) or not losing consciousness at the time of the injury (*bootstrap 95% CI* = -.07, .00). When exploring the moderating role of sustaining single or multiple TBI-related injury events, results suggested that PCL-M scores did not differentially mediate relations between NSI scores and cumulative disease burden as a function of either sustaining a single brain injury event (*bootstrap 95% CI* = -.10, .00) or sustaining multiple injury events (*bootstrap 95% CI* = -.06, .02). As discussed in previous sections, moderated mediation analyses were not conducted using system disease burden or SF-36 PCS variables as dependent variables given that the basic conditions for mediation were not satisfied.

Principal Axis Factoring

To explore whether mediational models could be replicated after removing nonspecific symptoms from the postconcussive and PTSD symptom variables, principal axis factoring with varimax rotation was used to first identify which symptoms most uniquely represent the postconcussive and PTSD syndromes. Three factors were specified to be extracted based on a priori hypotheses that items would cluster into three factors: postconcussive symptoms, PTSD symptoms, and symptoms loading onto both factors. Results of this factor analysis are presented in Table 10. Factor loadings above .40 were used to determine whether an item loaded onto any given factor.

Table 10

Three-Factor Principal Axis Factor Loadings for NSI and PCL-M Items

Indicator	Factor 1	Factor 2	Factor 3
Neurobehavioral Symptom Inventory			
Dizziness	.08	**.75**	.25
Loss of Balance	.09	**.69**	.29
Poor Coordination/Clumsy	.13	**.65**	.39
Headache	.17	**.62**	.12
Nausea	.15	**.70**	.05
Vision Problems/Blurring	.10	**.48**	.21
Sensitivity to Light	.21	**.55**	.28
Hearing Difficulty	.18	**.46**	.07
Sensitivity to Noise	.20	**.44**	.29
Numbness in Parts of Body	.15	**.62**	-.07
Change in Taste/Smell	.26	**.63**	.16
Change in Appetite	.26	**.57**	.22
Poor Concentration	.21	**.50**	**.62**
Forgetfulness	.21	**.63**	**.53**
Decision-Making Difficulty	.32	**.51**	**.60**
Slowed Thinking	.15	**.52**	**.70**
Fatigue/Loss of Energy	.18	**.55**	.38
Disturbed Sleep	.34	.38	.24

(*table continues*)

Table 10. (continued)

Three-Factor Principal Axis Factor Loadings for NSI and PCL-M Items

Indicator	Factor 1	Factor 2	Factor 3
Anxiety	**.44**	**.41**	**.43**
Depression	**.45**	.34	**.53**
Irritability	.37	.38	**.54**
Poor Frustration Tolerance	.36	.37	**.66**
PTSD Checklist			
Intrusive Thoughts	**.74**	.23	.32
Recurrent Dreams	**.68**	.27	.14
Flashbacks	**.66**	.37	.22
Emotional Reactivity	**.77**	.24	.31
Physiological Reactivity	**.67**	.31	.20
Avoidance of Thoughts	**.78**	.08	.31
Avoidance of Cues	**.85**	.12	.17
Psychogenic Amnesia	**.41**	.17	.36
Loss of Interest	**.48**	.22	**.63**
Feeling Detached from Others	**.54**	.18	**.62**
Emotionally Numb	**.45**	.10	**.61**
Sense of Foreshortened Future	**.47**	.09	**.62**
Disturbed Sleep	**.42**	.36	.28
Irritability	**.54**	.16	**.54**

(*table continues*)

Table 10. (continued)

Three-Factor Principal Axis Factor Loadings for NSI and PCL-M Items

Indicator	Factor 1	Factor 2	Factor 3
Poor Concentration	**.41**	.27	**.68**
Hypervigilance	**.58**	.30	.39
Exaggerated Startle	**.59**	.21	**.50**

Note. Results based on a sample size of n = 80. Rotated factor loadings above .40 are bolded.

Hypothesis 3a. Consistent with our hypotheses, somatic/sensory symptoms from the NSI generally loaded onto a factor representing postconcussive symptoms. These included items assessing dizziness, loss of balance, poor coordination, headaches, nausea, vision problems, sensitivity to light, hearing difficulty, sensitivity to noise, numbness in parts of the body, change in taste/smell, change in appetite, and fatigue. Furthermore, reexperiencing and avoidance symptoms from the PCL-M generally loaded onto a factor representing PTSD symptoms. These included intrusive thoughts, recurrent dreams, flashbacks, emotional and physiological reactivity, and avoidance of thoughts and cues associated with trauma. Interestingly, the psychogenic amnesia item from the PCL-M also loaded onto the PTSD factor. Hyperarousal symptoms including disturbed sleep and hypervigilance also loaded onto the PTSD factor, although the item assessing disturbed sleep was not included in the computation of the new PTSD variable given that the NSI and PCL-M both contain items assessing sleep disturbance. The remaining items either loaded onto a third factor representing nonspecific symptoms or cross-loaded onto more than one factor. These items included the poor concentration, forgetfulness, decision-making difficulty, slowed thinking, anxiety, depression, irritability, and poor frustration tolerance items from the NSI along with the loss of interest, feeling detached from others, emotionally numb, sense of foreshortened future, irritability, poor concentration, and exaggerated startle items from the PCL-M. The disturbed sleep item from the NSI did not load onto any factors. NSI and PCL-M items loading onto the postconcussive symptom and PTSD factors were summed to create new symptom variables – a postconcussive symptom variable and a PTSD variable, and these variables were used to replicate each of the mediational models.

Hypothesis 3b. Prior to testing mediational models, bivariate associations between the postconcussive symptom factor, the PTSD factor, health outcomes, substance use behaviors, and demographic variables were examined and are presented in Table 11. A statistically significant association was found between the postconcussive symptom factor and the PTSD factor ($r = .55$, $p < .01$). Cumulative disease burden was associated with both the postconcussive ($r = .56$, $p < .01$) and PTSD ($r = .30$, $p < .01$) symptom factors. However, only the postconcussive symptom factor evidenced statistically significant associations with system disease burden. So, as with our primary analyses, mediation analyses were not conducted using system disease burden as the dependent variable since the basic conditions for mediation were not satisfied.

***Mediation analyses*.** A mediation analysis was conducted to test whether the PTSD factor mediated associations between the postconcussive symptom factor and cumulative disease burden. These results are presented in Table 12. No statistically significant direct effect emerged between the PTSD factor and cumulative disease burden. However, a statistically significant direct effect emerged between the postconcussive symptom factor and cumulative disease burden after modeling

Table 11

Bivariate Correlations between Postconcussive Symptom, PTSD, Health, and Demographic Variables after Removing Nonspecific Symptoms from the Postconcussive and PTSD Variables

Variables	1	2	3	4	5	6	7	8	9	10
1. PCS	--	.55**[b]	.07[b]	.01	.56**	.38**	-.42**[d]	-.11	.18[†]	.10[a]
2. PTSD		--	.39**[c]	.01[b]	.30**[b]	.08[b]	-.17[e]	-.03[b]	.04[b]	.03[c]
3. AUDIT			--	--	--	--	--	--	--	--
4. TOB				--	--	--	--	--	--	--
5. CDB					--	--	--	--	--	--
6. SDB						--	--	--	--	--
7. PHYS							--	--	--	--
8. Gender								--	--	--
9. Age									--	--
10. MAR										--

Note. PCS = Postconcussive symptom variable computed using items loading onto the postconcussive symptom factor; PTSD = PTSD symptom variable computed using items loading onto the PTSD symptom factor; AUDIT = Alcohol Use Disorders Identification Test; TOB = VA Tobacco Screen; CDB = Cumulative Disease Burden; SDB = System Disease Burden; PHYS = SF-36 Physical Component Summary; MAR = Marital Status. AUDIT scores in these analyses were transformed using square-root transformations.
[a]*n* = 90. [b]*n* = 89. [c]*n* = 88. [d]*n* = 82. [e]*n* = 81. [†] *p* < .10. **p* < .05. ***p* < .01.

associations with the PTSD factor. Furthermore, bootstrap estimates of the indirect effect suggest that the PTSD factor did not mediate relations between the postconcussive symptom factor and cumulative disease burden.

Table 12

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Health Outcomes after Removing Nonspecific Symptoms

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Cumulative Disease Burden (n = 89)			.32			
c (PCS → CDB)	.16**	.02				
a (PCS → PTSD)	.49**	.08				
b (PTSD → CDB)	-.01	.03				
c´	.16**	.03				
a x b				-.00	.02	-.04, .02

Note. NSI = PCS = Postconcussive symptom variable computed using items loading onto the postconcussive symptom factor; PTSD = PTSD symptom variable computed using items loading onto the PTSD symptom factor; CDB = Cumulative Disease Burden.
† $p < .10$. *$p < .05$. **$p < .01$.

In reverse mediation analyses using symptom variables composed of items loading onto each factor, statistically significant direct effects emerged between the postconcussive symptom factor and cumulative disease burden. These results are presented in Table 13. A statistically significant direct effect also emerged between the

PTSD factor and cumulative disease burden, although this effect was no longer significant after modeling associations with the postconcussive symptom variable. In addition, bootstrap estimates of the indirect effect suggest that the postconcussive symptom factor fully mediated relations between the PTSD factor and cumulative disease burden.

Table 13

Regression Analyses with Bootstrap Estimates: Postconcussive Symptoms Mediating Relations between PTSD and Health Outcomes after Removing Nonspecific Symptoms

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Cumulative Disease Burden (n = 89)			.32			
c (PTSD → CDB)	.09**	.03				
a (PTSD → PCS)	.62**	.10				
b (PCS → CDB)	.16**	.03				
c´	-.01	.03				
a x b				.10	.03	.05, .17

Note. PCS = Postconcussive symptom variable computed using items loading onto the postconcussive symptom factor; PTSD = PTSD symptom variable computed using items loading onto the PTSD symptom factor; CDB = Cumulative Disease Burden.
† $p < .10$. *$p < .05$. **$p < .01$.

Mediation analyses with ICD-9-CM categories. A series of mediational analyses were also conducted to explore whether PTSD symptoms mediated relations between postconcussive symptoms and specific *ICD-9-CM* major medical categories after removing nonspecific symptoms from the computation of PCL-M and NSI scores. Results are presented in Table 14.

Table 14

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories after Removing Nonspecific Symptoms

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Endocrine, Nutritional, and Metabolic Diseases and Nutritional Disorders[a]			.07			
c (PCS → ENM)	.00*	.00				
a (PCS → PTSD)	.49**	.08				
b (PTSD → ENM)	-.00	.00				
c´	.00*	.00				
a x b				-.00	.00	-.00, .00
Diseases of the Nervous System and Sense Organs[b]			.05			
c (PCS → NRV)	.01*	.01				

(*table continues*)

Table 14. (continued)

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories after Removing Nonspecific Symptoms

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	*R²*	*B*	*SE*	*95% CI*
a (PCS → PTSD)	.49**	.08				
b (PTSD → NRV)	-.01	.01				
c´	.02[†]	.01				
a x b				-.00	.00	-.01, .01
Diseases of the Circulatory System[c]						
c (PCS → CIR)	.00	.03				
a (PCS → PTSD)	.49**	.08				
b (PTSD → CIR)	-.02	.04				
c´	.01	.03				
a x b				-.01	.02	-.06, .02
Diseases of the Respiratory System[b]			.01			
c (PCS → RES)	.00	.00				
a (PCS → PTSD)	.49**	.08				
b (PTSD → RES)	-.00	.00				

(*table continues*)

Table 14. (continued)

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories after Removing Nonspecific Symptoms

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
c´	.00	.00				
a x b				-.00	.00	-.00, .00
Diseases of the Digestive System[b]			.14			
c (PCS → DIG)	.01**	.00				
a (PCS → PTSD)	.49**	.08				
b (PTSD→ DIG)	-.00	.00				
c´	.01**	.00				
a x b				.00	.00	-.00, .00
Diseases of the Musculoskeletal System and Connective Tissue[a]			.06			
c (PCS → MUSC)	.02*	.01				
a (PCS → PTSD)	.49**	.08				
b (PTSD → MUSC)	-.00	.01				
c´	.02[†]	.01				

(*table continues*)

Table 14. (continued)

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Disease Categories after Removing Nonspecific Symptoms

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
a x b				.00	.00	-.01, .01
Symptoms, Signs, and Ill-Defined Conditions[a]			.13			
c (PCS → ILL)	.02**	.01				
a (PCS → PTSD)	.49**	.08				
b (PTSD → ILL)	.00	.01				
c´	.02**	.01				
a x b				.00	.00	-.01, .01
Mental Disorders[a]			.27			
c (PCS → MEN)	.03**	.01				
a (PCS → PTSD)	.49**	.08				
b (PTSD → MEN)	.01[†]	.01				
c´	.02**	.01				
a x b				.01	.00	-.00, .01

Note. PCS = Postconcussive symptom variable computed using items loading onto the postconcussive symptom factor; PTSD = PTSD symptom variable computed using items loading onto the PTSD symptom factor; ENM = Endocrine, Nutritional, and Metabolic Diseases and Immunity Disorders; NRV = Diseases of the Nervous System and Sense Organs; CIR = Diseases of the Circulatory System; RES = Diseases of the Respiratory System; DIG = Diseases of the Digestive System; MUSC = Diseases of the

Musculoskeletal System and Connective Tissue; ILL = Symptoms, Signs, and Ill-Defined Conditions; MEN = Mental Disorders. N = 89 for all analyses.
[a]Variable transformed using log transformations.
[b]Variable transformed using square-root transformations.
[c]Given that no Veterans had more than one circulatory system disorder, the dependent variable was binary, and a logistic regression model was used for the analysis. However, R^2 cannot be derived for non-linear models and is unavailable.
† $p < .10$. *$p < .05$. **$p < .01$.

After removing nonspecific symptoms, the postconcussive symptom factor was independently associated with endocrine, nutritional, and metabolic diseases and immunity disorders, nervous system diseases, digestive conditions, musculoskeletal diseases, and idiopathic complaints. However, after removing postconcussive symptoms assessed on the NSI from the idiopathic complaints variable, the postconcussive symptom factor was no longer associated with idiopathic complaints (see Table 15). No statistically significant direct effect was found between the PTSD factor and any of the major medical categories, including the idiopathic complaints variable with postconcussive symptoms removed. So, the PTSD factor did not appear to mediate relations between the postconcussive symptom factor and any major medical category when nonspecific symptoms were excluded from the computation of the postconcussive and PTSD symptom variables. We also conducted analyses examining whether the PTSD factor mediated relations between the postconcussive symptom factor and mental health diagnoses after removing nonspecific symptoms. The postconcussive symptom factor was independently associated with mental health diagnoses after modeling associations with the PTSD factor. The PTSD factor, however, was not directly associated with mental health diagnoses and, thus, did not appear to mediate relations between the postconcussive symptom factor and mental health diagnoses even after removing nonspecific symptoms from both variables.

Table 15

Regression Analyses with Bootstrap Estimates: PTSD Mediating Relations between Postconcussive Symptoms and Idiopathic Complaints after Removing Complaints Shared with the NSI from the Idiopathic Complaints Variable and Removing Nonspecific Symptoms from the PTSD and Postconcussive Variables

	Regression Results			Bootstrap Estimates		
Path/Effect	*B*	*SE*	R^2	*B*	*SE*	*95% CI*
Symptoms, Signs, and Ill-Defined Conditions[a] (*n* = 89)			.02			
c (NSI → ILL)	.00	.00				
a (NSI → PCL-M)	.49**	.08				
b (PCL-M → ILL)	-.00	.00				
c´	.00	.00				
a x b				-.00	.00	-.00, .00

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; ILL = Symptoms, Signs, and Ill-Defined Conditions.
[a]Variable transformed using log transformations.
† $p < .10$. *$p < .05$. **$p < .01$.

***Mediation analyses with substance use behaviors*.** Mediation analyses were not conducted exploring whether the PTSD factor mediated relations between the postconcussive symptom factor and substance use behaviors (i.e., alcohol and tobacco use) given that the postconcussive symptom factor was not associated with AUDIT scores or tobacco use (see Table 11). Therefore, the basic conditions for mediation were not satisfied.

Moderated mediation analyses. Lastly, we explored whether our mediational model was conditional as a function of characteristics associated with the injury after removing nonspecific symptoms from the PCL-M and NSI variables. Results are presented in Table 16. The PTSD factor did not differentially mediate relations between

Table 16

Moderated Mediation Analyses as a Function of Losing Consciousness and Sustaining Multiple Injuries after Removing Nonspecific Symptoms from Postconcussive Symptom and PTSD Variables: Cumulative Disease Burden

		Conditional Indirect Effect	*SE*	*Z*
Loss of Consciousness[a]	LOC	.00	.04	.03
	No LOC	.00	.02	.20
Number of mTBIs[b]	1 mTBI	-.00	.02	-.13
	> 1 mTBI	.00	.02	.21

[a]$n = 89$. [b]$n = 88$.
† $p < .10$. *$p < .05$. **$p < .01$.

the postconcussive symptom factor and cumulative disease burden as a function of losing consciousness (*bootstrap 95% CI* = -.12, .06) or not losing consciousness (*bootstrap 95% CI* = -.03, .03). Likewise, the PTSD factor did not differentially mediate relations between the postconcussive symptom factor and cumulative disease burden as a function of either sustaining a single brain injury event (*bootstrap 95% CI* = -.07, .02) or sustaining multiple brain injury events (*bootstrap 95% CI* = -.05, .04). Moderated mediation analyses using system disease burden or SF-36 PCS variables as dependent variables were not pursued given that the basic conditions for mediation were not satisfied.

Hypothesis 3c. Only the postconcussive symptom factor, and not the PTSD factor, evidenced statistically significant associations with SF-36 PCS scores. So, a mediation analysis was not conducted using SF-36 PCS scores as a dependent variable since the basic conditions for mediation were not satisfied.

Path Analyses

Hypothesis 4a. A path analysis was conducted to examine structural relations between postconcussive and PTSD symptoms, substance abuse, and health outcomes. Figure 4 depicts the results of the expected model proposed in Figure 3.

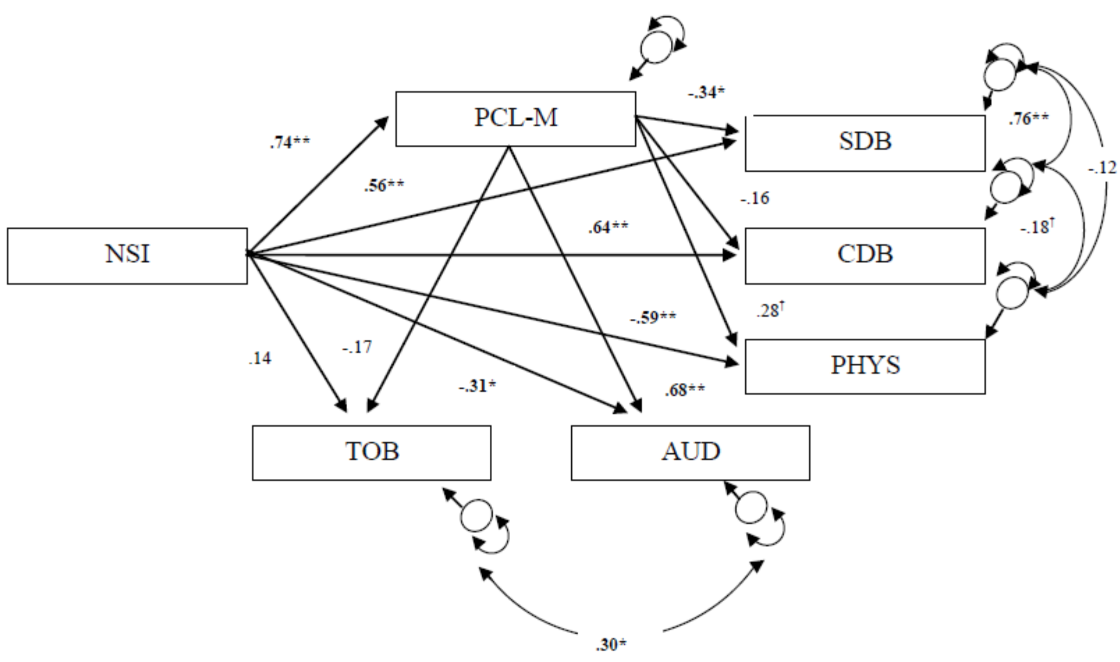

Figure 4. Multivariate model including postconcussive symptoms, PTSD, substance use behaviors and health outcomes.

Note. NSI = Neurobehavioral Symptom Inventory; PCL-M = PTSD Checklist; AUD = Alcohol Use Disorders Identification Test; TOB = VA Tobacco Screen; SDB = system disease burden; CDB = cumulative disease burden; PHYS = SF-36 Physical Component Summary. AUDIT scores in these analyses were transformed using square-root transformations.
† $p < .10$. *$p < .05$. **$p < .01$.

A visual inspection of the fit statistics suggests that the model is an excellent fit for the data ($\chi^2(6) = 6.65$, $p > .25$; *RMSEA* = .04; *CFI* = 1.00; *TLI* = .99). NSI scores were a statistically significant predictor of PCL-M scores and each health outcome (i.e., cumulative disease burden, system disease burden, and SF-36 PCS scores). NSI scores were also a statistically significant predictor of AUDIT scores although the path coefficient was negative, suggesting that higher NSI scores are associated with lower AUDIT scores. Neither NSI scores nor PCL-M scores were associated with tobacco use. PCL-M scores were a statistically significant predictor of AUDIT scores. In terms of health outcomes, the paths between PCL-M scores and cumulative disease burden and PCS scores were non-significant. However, the path between PCL-M scores and system disease burden was statistically significant in the structural model.

The model was also tested using postconcussive and PTSD symptom variables computed using only those items that loaded onto the postconcussive and PTSD factors. Figure 5 depicts the results of this model using the postconcussive and PTSD symptom factors. A visual inspection of the fit statistics suggests that this model is an excellent fit for the data ($\chi^2(6) = 5.22$, $p > .25$; *RMSEA* = .00; *CFI* = 1.00; *TLI* = 1.02). As with the previous model, the postconcussive symptom factor was a statistically significant predictor of PTSD, each health outcome (i.e., cumulative disease burden, system disease

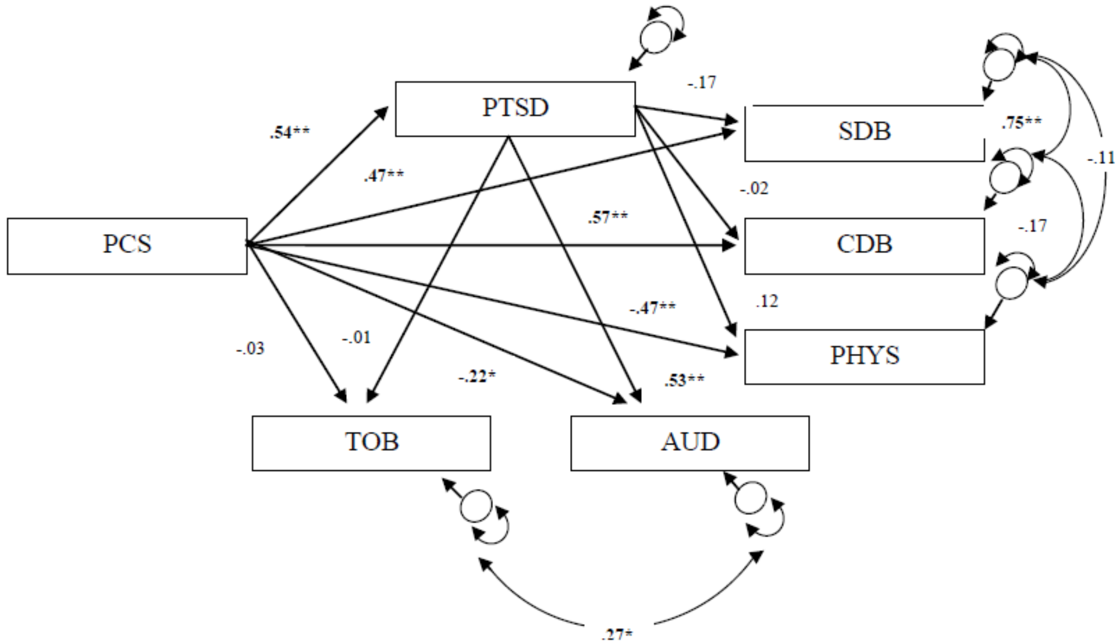

Figure 5. Multivariate model including postconcussive symptoms, PTSD, substance use behaviors and health outcomes after removing nonspecific symptoms from postconcussive symptom and PTSD variables.

Note. PCS = Postconcussive symptom variable computed using items loading onto the postconcussive symptom factor; PTSD = PTSD symptom variable computed using items loading onto the PTSD symptom factor; AUD = Alcohol Use Disorders Identification Test; TOB = VA Tobacco Screen; SDB = system disease burden; CDB = cumulative disease burden; PHYS = SF-36 Physical Component Summary. AUDIT scores in these analyses were transformed using square-root transformations.
† $p < .10$. *$p < .05$. **$p < .01$.

burden, and SF-36 PCS scores), and AUDIT scores. The path between the PTSD factor and AUDIT scores was statistically significant, but neither the PTSD factor nor postconcussive symptom factor were associated with tobacco use. In contrast to the previous model, the PTSD factor was not associated with any health outcome, including system disease burden.

Summary

Of the 573 OEF/OIF Veterans screened as part of the current study, 120 (21.8%) screened positive for mTBI. The majority of Veterans (*n* = 95, 79.2%) screening positive for mTBI completed second level, Polytrauma Clinic evaluations for TBI. Valid data were available for 91 Veterans completing Polytrauma TBI evaluations. Among these Veterans, large, statistically significant associations emerged between Neurobehavioral Symptom Inventory (NSI) scores (a self-report measure of persistent, postconcussive symptoms) and PCL-M scores (a self-report measure of PTSD symptoms). Both NSI and PCL-M scores were associated with cumulative disease burden, but only NSI scores were associated with system disease burden and SF-36 Physical Component Summary scores (a self-report measure of physical health functioning).

In testing a mediational model where PCL-M scores were modeled as a mediator between NSI scores and cumulative disease burden, results suggested that the association between NSI scores and cumulative disease burden was independent of PCL-M scores and that PCL-M scores did not mediate this association. Reverse analyses similarly suggested that NSI scores fully mediated associations between PCL-M scores and cumulative disease burden. A series of exploratory mediational models revealed that NSI scores were independently associated with several categories of medical conditions, including endocrine, nutritional, and metabolic diseases and immunity disorders, digestive conditions, and idiopathic complaints, and these associations were not mediated by PCL-M scores. However, neither NSI scores nor PCL-M scores were associated with idiopathic complaints after removing postconcussive symptoms from the idiopathic complaints variable. Moreover, PCL-M scores did not seem to differentially mediate associations between NSI scores and cumulative disease burden as a function of either losing consciousness at the time of an injury or sustaining multiple brain injury-related events.

Because somatic/sensory symptoms most uniquely represented the persistent, postconcussive symptom factor and reexperiencing and avoidance symptoms most uniquely represented the PTSD factor, postconcussive and PTSD symptom variables composed of these unique items were created and used to replicate the mediational models. The same pattern of results emerged whereby unique postconcussive symptoms were independently associated with cumulative disease burden after modeling associations with unique PTSD symptoms, and PTSD symptoms did not appear to mediate this association. Moreover, unique PTSD symptoms did not differentially mediate associations between postconcussive symptoms and cumulative disease burden as a function of either losing consciousness at the time of an injury or sustaining multiple brain injury-related events.

Lastly, a path analysis exploring structural relations between postconcussive symptoms, PTSD, substance use behaviors, and health outcomes supported findings that postconcussive symptoms were independently associated with each health outcome (i.e., cumulative disease burden, system disease burden, and SF-36 PCS scores). This association was not mediated by either PTSD or substance use behaviors.

Chapter 4

Discussion, Conclusions and Recommendations

Treating Veterans of Operations Enduring and Iraqi Freedom poses special challenges for health care providers in that these Veterans are at increased risk for a variety of often co-occurring physical and mental health problems, including persistent postconcussive symptoms, PTSD, and substance misuse. Understanding how these problems uniquely impact health and health functioning may be beneficial to clinicians in terms of treatment planning for Veterans presenting with complex clinical profiles. The current study suggests that, among those Veterans with a history of deployment-related TBI, residual postconcussive symptoms may have an especially adverse impact on health. Before turning to a discussion of the clinical implications of these findings, we will first consider the findings within the broader context of research on TBI, postconcussive symptoms, PTSD, and health.

Sample Characteristics

The rate of positive mTBI screens in the full sample was consistent with rates reported in similar samples of OEF/OIF Veterans seeking VA health care (e.g., Carlson et al., 2010). Moreover, the mean PCL-M and AUDIT scores for the full sample were also comparable to scores reported in other samples of OEF/OIF Veterans enrolled in VA health care (e.g., Erbes et al., 2007). The rate of current tobacco use for the full sample, on the other hand, was somewhat elevated (42.8%) relative to other samples of treatment-seeking OEF/OIF Veterans (e.g., 25.2% current smoking rate reported by Jakupcak et al., 2008), although the rate may be more comparable to rates observed among active duty personnel more generally. For example, in a large sample of active duty personnel, Bray et al. (2006) found that roughly one-third (31%) of active duty military personnel reported currently smoking, and approximately 14% report using smokeless tobacco. Together, these rates may be more in line with those reported in the current study, which utilized a screen that assessed for any tobacco use, including use of cigarettes and smokeless tobacco. Given that Possemato et al. (2010) did not report descriptive statistics for cumulative and system disease burden in their sample, we are aware of no studies that have reported comparable disease burden rates for OEF/OIF Veterans. However, the mean PCS score assessing self-reported physical health functioning in the full sample was comparable to mean PCS scores reported in a separate sample of OEF/OIF Veterans recruited from the same VA clinic (McDevitt-Murphy et al., 2010).

Among the subset of 91 Veterans completing Polytrauma evaluations for TBI who were the focus of the current study, mean NSI scores were generally more severe than NSI scores reported in other samples of OEF/OIF Veterans with a history of deployment-related TBI (e.g., Belanger et al., 2009). Mean PCL-M scores were also higher in this subset of Veterans compared to the full sample – the mean PCL-M score of 54 among these Veterans is above the commonly used PCL-M cut-score of 50 used to identify individuals screening positive for PTSD (Ruggiero, Del Ben, Scotti, & Rabalais, 2003). The presence of more severe PTSD symptoms may help contextualize the higher NSI scores reported by Veterans completing these Polytrauma evaluations. For example, Cooper et al. (2011), in a sample of OEF/OIF Veterans screening positive for a history of mTBI, reported that Veterans with high combat stress (defined as greater than or equal to 60 on the PCL) evidenced significantly more postconcussive symptoms than Veterans with low combat stress (less than or equal to 30 on the PCL).

Consistent with the trend of more severe symptomatology among Veterans screening positive for mTBI and completing Polytrauma evaluations, these Veterans reported engaging in higher levels of alcohol and tobacco use relative to the full sample. These Veterans also tended to have more medical conditions across a greater number of distinct physical systems than Veterans in the full sample, and the most commonly documented physical conditions among Veterans completing Polytrauma evaluations were idiopathic complaints, musculoskeletal conditions, and nervous system disorders. Similarly, these Veterans reported more functional health impairment due to physical health than Veterans in the full sample.

Relations Between Variables

As expected, NSI scores were strongly associated with PCL-M scores, an association that has been documented in similar samples of OEF/OIF Veterans (e.g., King et al., 2012). The association between NSI scores and each health outcome, including both cumulative and system disease burden and SF-36 PCS scores was also expected, but a more puzzling finding is that PCL-M scores were only associated with cumulative disease burden. Several factors may explain this pattern of results. For instance, Possemato and colleagues (2010) found that, upon entry into the VA, having a diagnosis of PTSD was associated with increased medical morbidity across multiple medical categories (i.e., system disease burden) but that, across time, PTSD was more associated with a rapid accumulation of medical conditions overall (i.e., cumulative disease burden) than across new medical categories. In other words, Veterans with PTSD may be more likely to accumulate diseases within medical categories that are already positive for at least one medical condition, at least during the years immediately following deployment. Since the cumulative and system disease burden variables used in this study were aggregates of clinician diagnosed conditions accumulated over the course of the year following entry into the VA system, the way in which these variables were constructed may obscure any time-dependent associations between PCL-M scores and system disease burden.

In terms of the association with substance use disorders, PCL-M scores were associated with AUDIT scores, although, contrary to our hypotheses, no statistically significant association was observed between NSI scores and AUDIT scores. This finding is not entirely surprising, however, in light of recent evidence suggesting that Veterans with a history of mTBI do not necessarily engage in a different pattern of alcohol use relative to those without a history of mTBI (e.g., Williams et al., 2012). The absence of a hypothesized association between NSI and PCL-M scores and tobacco use seems less clear, but the elevated NSI and PCL-M scores and rate of tobacco use in this sample suggests a somewhat restricted range of severity in that these Veterans tended to be more severe across all three domains. Perhaps both NSI and PCL-M scores would be associated with tobacco use in samples of Veterans with a wider range of postconcussive and PTSD symptom severity. Results did not support the hypothesis that substance use behaviors are associated with health outcomes, including both disease burden variables and SF-36 PCS scores. However, Veterans in this study were generally young and likely not exhibiting the long-term effects of chronic substance abuse.

Mediational Models

In the absence of statistically significant associations between PCL-M scores and system disease burden and SF-36 PCS scores, mediational models were not testing using either of these health outcomes as dependent variables. A mediational model was tested to explore whether PCL-M scores mediated relations between NSI scores and cumulative disease burden, and, contrary to our hypothesis, PCL-M scores did not mediate relations between NSI scores and cumulative disease burden. So, these results fail to support the theory that postconcussive symptoms indirectly contribute to disease burden by increasing risk for PTSD and PTSD-related health problems. Rather, these results suggest that persistent, postconcussive symptoms are uniquely associated with the overall accumulation of clinician-diagnosed medical conditions. However, this pattern of results is somewhat consistent with previous research indicating that a history of mTBI is uniquely associated with health even after accounting for the adverse health impact of PTSD (e.g., Pietrzak et al., 2009; Vasterling et al., 2012). Although PTSD may not fully (or partially) explain this association, the results of our reverse mediational analysis suggest that PTSD may still be an important factor to consider in understanding the unique association between postconcussive symptoms and health. In our reverse mediational analysis, for example, PCL-M scores were associated with higher NSI scores, and the association between PCL-M scores and cumulative disease burden was fully mediated by NSI scores. That is, PTSD may increase risk for persistent, postconcussive symptoms and associated health problems.

While this pattern of results was unexpected, these findings may provide some support for the theory that PTSD symptoms play a critical role in inhibiting long-term recovery after sustaining an mTBI. Both mTBI and PTSD are thought to disrupt prefrontal cortical functioning (Bigler & Maxwell, 2012; Otis et al., 2012), in the case of mTBI because prefrontal cortical regions may be especially susceptible to biomechanical forces such as blast waves (e.g., Stein & McAllister, 2009). Prefrontal cortical regions of the brain are thought to be associated with the ability to regulate emotional responses such as fear (see Hayes & Gilbertson, 2012, for a review of the neuroanatomical circuitry underlying PTSD) as well as perceived physiological pain. For example, in an fMRI study on the perceived controllability of pain, Salomons, Johnstone, Backonja, Shakman, and Davison (2007) reported that activation of two prefrontal clusters – the pregenual anterior cingulated cortex and the ventral lateral prefrontal cortex – predicted up to 64% of variance in pain rating differences following an experimental presentation of thermal heat stimuli. PTSD is also associated with increased somatosensory cortical activation during regulatory processing, which may decrease regulatory efficiency in the prefrontal cortex. For instance, Falconer et al. (2008), examining response inhibition during fMRI scanning, found that, relative to healthy controls, individuals with PTSD were observed to have less activation in the ventrolateral prefrontal cortex during regulatory processing, although they were observed to have more somatosensory and visual cortical activation than control subjects. Falconer and colleagues note that this cortical hyperexcitability may lead to excessive sensitivity to various stimuli and thereby undermine efforts to effectively regulate sensory input. So, the emergence of PTSD symptoms following an initial neurobiological injury may decrease an individual's ability to regulate somatic/sensory and affective symptoms following a brain injury such that these symptoms do not fully resolve, even in the absence of persistent neurological damage.

As PTSD may inhibit the resolution of somatic and sensory postconcussive symptoms following a brain injury, Veterans may be more likely to report these symptoms to health care providers upon initiating treatment in the VA system, resulting in greater overall accumulation of documented somatic complaints of unknown origin. Indeed, idiopathic complaints (including dizziness, disturbance of skin sensation, and disturbed sleep) were the most commonly diagnosed conditions in this sample. Moreover, in analyses exploring relations between postconcussive symptoms, PTSD, and each *ICD-9-CM* major medical category, NSI scores were independently associated with idiopathic complaints after controlling for PCL-M scores. NSI scores were not, however, associated with the accumulation of idiopathic complaints after removing postconcussive symptoms commonly coded by clinicians as idiopathic complaints. That is, after postconcussive symptoms, such as headache, dizziness, and numbness in parts of the body, were removed from the idiopathic complaints variable, NSI scores were no longer associated with idiopathic complaints.

NSI scores were also independently associated with endocrine, nutritional, and metabolic diseases and immunity disorders and digestive conditions after controlling for PCL-M scores. While previous research has found evidence of an association between blast-related mTBI and neuroendocrine alterations in the acute, post-injury phase (Cernak, Savic, Lazarov, Joksimovic, & Markovic, 1999), interpreting the association between NSI scores and endocrine, nutritional, and metabolic diseases in this sample is limited by the fact that only 14 Veterans were diagnosed with these conditions. In terms of the association between NSI scores and digestive conditions, physical trauma sustained at the time of the injury may underlie this association. The digestive tract and air-filled organs such as the bowel and lungs are thought to be highly susceptible to blast-related injuries (Taber et al., 2006). NSI scores were also independently associated with mental disorders after controlling for PCL-M scores. This finding is not terribly surprising, though, given that sustaining an mTBI has been associated with a number of poor mental health outcomes beyond PTSD, especially depression (Iverson, 2012).

Loss of consciousness at the time of the injury was expected to moderate the mediational models since some research suggests that an inability to recall traumatic experiences may reduce risk for experiencing PTSD symptoms, such as reexperiencing symptoms (e.g., Hayes & Gilbertson, 2012). In moderated mediation analyses, neither loss of consciousness at the time of the injury nor sustaining multiple brain injury events moderated the pattern of mediation whereby NSI scores were independently associated with cumulative disease burden after modeling associations with the PCL-M. Although previous research suggests that mTBI is associated with adverse health outcomes, especially when loss of consciousness occurs at the time of the injury (e.g., Hoge et al., 2008; Ishibe, Wlordarczyk, & Fulco, 2009), these results suggest that the association between mTBI and adverse health outcomes may be constant. That is, the association between mTBI and health outcomes does not seem to be either partially or fully accounted for by PTSD, regardless of whether the injury was severe enough to produce unconsciousness or whether the Veteran sustained multiple brain injury events. So, having a memory of a head injury event does not seem to affect whether PTSD symptoms better account for the association between postconcussive symptoms and health outcomes.

Symptom Factors and Replicated Mediation Models

In order to test the robustness of these models, especially given the large proportion of symptoms shared between postconcussive syndrome and PTSD, factor analytic strategies were used to identify those symptoms most unique to each construct –

information that was then used to create new postconcussive and PTSD symptom variables with nonspecific symptoms removed. Consistent with our hypothesis, somatic/sensory symptoms from the NSI, including dizziness, headache, and nausea, most uniquely represented the postconcussive symptom factor. This finding generally supports previous research suggesting that somatic symptoms are most uniquely associated with a history of mTBI after adjusting for other psychiatric and medical diagnoses (e.g., Vanderploeg et al., 2009). Also consistent with our hypothesis, reexperiencing symptoms from the PCL-M, including intrusive memories of traumatic events, nightmares, and physiological reactivity to trauma-related cues, loaded onto a PTSD factor along with the avoidance (i.e., avoidance of thoughts, avoidance of cues), psychogenic amnesia, and hypervigilance symptoms. Although we did not initially hypothesize that the avoidance and hypervigilance items would load onto the PTSD factor, previous research with civilian trauma survivors has supported such a model whereby PTSD is uniquely associated with reexperiencing, avoidance, and hypervigilance symptoms (Grant, Beck, Marques, Palyo, & Clapp, 2008).

Cognitive and emotional symptoms from both the NSI and PCL-M (including items such as decision-making difficulty and forgetfulness from the NSI and loss of interest and emotional numbing from the PCL-M) tended to cross-load onto more than one factor or load onto a third, nonspecific symptom factor. This finding supports previous research suggesting that cognitive and emotional postconcussive symptoms are not specifically associated with a history of mTBI after adjusting for psychiatric and medical disorders like PTSD (e.g., Vanderploeg et al., 2009). Recent factor analytic research involving OEF/OIF Veterans seeking VA primary care also supports the finding that symptoms such as loss of interest in activities, emotional numbing, irritability, and difficulty concentrating are not specific to PTSD (Williams, Monahan, & McDevitt-Murphy, 2011). After computing new postconcussive and PTSD symptom variables with these nonspecific symptoms removed, the initial mediation analysis was replicated using these new variables. Again, the PTSD factor did not mediate relations between the postconcussive symptom factor and cumulative disease burden, suggesting that the greater accumulation of medical diagnoses associated with postconcussive symptoms is driven, in large part, by postconcussive somatic/sensory complaints.

The reverse mediation analysis was also replicated using the new postconcussive and PTSD symptom variables, and, as with the original analysis, the postconcussive symptom factor fully mediated associations between the PTSD factor and cumulative disease burden. In other words, symptoms unique to the PTSD factor were associated with an increased risk of somatic/sensory postconcussive complaints and associated health problems. Moreover, mediation analyses exploring relations between the postconcussive symptom factor, PTSD factor, and each *ICD-9-CM* major medical category revealed the same pattern of findings that emerged using the full NSI and PCL-M variables. That is, after modeling associations with the PTSD factor, the postconcussive symptom factor was independently associated with endocrine, nutritional, and metabolic diseases and immunity disorders, digestive conditions, and idiopathic complaints, although the association with idiopathic complaints was no longer statistically significant after removing postconcussive symptoms from the computation of this variable. Together, these findings lend further support for a stress-maintenance model where PTSD symptoms may inhibit recovery from somatic/sensory postconcussive symptoms – symptoms that may be documented by health care providers as idiopathic complaints. Lastly, moderated mediation analyses using the postconcussive symptom and PTSD factor again failed to find evidence that the PTSD factor differentially mediated associations between the postconcussive symptom factor and cumulative disease burden as a function of injury characteristics, including loss of consciousness or sustaining multiple brain injury events.

Postconcussive Symptoms, PTSD, and Health – A Multivariate Model

The final set of analyses aimed to examine associations between postconcussive symptoms, PTSD, substance use behaviors (i.e., alcohol misuse and tobacco use), and health outcomes. After testing the full, anticipated model (Figure 3), the results were consistent with each of the previous analyses in that NSI scores were independently associated with each health outcome, even after modeling associations with PTSD and substance use behaviors. These results were replicated after running the analyses with the postconcussive and PTSD symptom variables with nonspecific symptoms removed. So, the association between persistent, postconcussive symptoms and subjective and objective health indices is not better explained by PTSD or substance misuse.

Summary

In sum, the results of this study support previous research suggesting that postconcussive symptoms are independently associated with poorer overall health and extend this research by examining the association between postconussive symptoms and objective health indices. Generally speaking, prior studies looking at the association between mTBI, PTSD, and health outcomes have conceptualized PTSD as a mediator of the association between mTBI and health. The current results, however, may provide an initial framework for a slightly different conceptualization – that residual mTBI, or persistent postconcussive, symptoms, may mediate the association between PTSD and health among Veterans with a history of both mTBI and PTSD. The basis for the initial conceptualization that PTSD at least partially mediates the association between mTBI, postconcussive symptoms, and health is founded, in large part, on research with civilian samples suggesting that sustaining an mTBI may increase risk for PTSD by taxing cognitive resources necessary to process trauma memories (e.g., Bryant, 2008). Indeed, when PTSD was modeled as a mediator in the current study, a strong, statistically significant association was found between postconcussive symptoms and PTSD, providing at least some support for this initial conceptualization. However, PTSD did not explain the association between postconcussive symptoms and cumulative disease burden, suggesting that a model where postconcussive symptoms increase risk for PTSD and PTSD-related health problems may be overly simplistic.

In our reverse analyses, however, PTSD did increase risk for postconcussive symptoms and associated health problems. Combined with the other results, this finding may provide supportive evidence for a stress-maintenance model where sustaining an mTBI may increase risk for PTSD, but as the initial neurological injury resolves, PTSD-related anxiety may inhibit the full resolution of postconcussive symptoms. As Veterans with persistent postconcussive symptoms and PTSD present to health care settings, they may then be more likely to endorse unresolved somatic/sensory postconcussive symptoms, which are then documented by clinicians as idiopathic complaints. Indeed, after removing nonspecific symptoms from the postconcussive and PTSD symptom variables, somatic/sensory postconcussive symptoms were independently associated with cumulative disease burden after modeling associations with PTSD.

As discussed previously, one potential mechanism underlying this pattern of results may lie in the executive dysregulation associated with PTSD. As PTSD results in greater executive dysfunction, the ability to regulate somatic complaints may become less efficient. However, neural pathways thought to be involved in mTBI and PTSD are also commonly associated with chronic pain (Otis et al., 2012), and the presence of comorbid postconcussive and PTSD symptoms may increase overall pain intensity throughout the body. In a review of the extant literature on comorbid pain and PTSD, Beck and Clapp (2011) note that attentional biases to pain and trauma-related cues may help maintain both chronic pain and PTSD such that pain sensations may cue trauma-related reexperiencing symptoms, thus enhancing attentional bias to pain sensations in a cyclical fashion. Beck and Clapp also note that anxiety sensitivity may be an important factor in understanding increased pain intensity associated with PTSD where individuals with PTSD may be more likely to interpret physical pain sensations as dangerous and threatening. So, Veterans with elevated PTSD symptoms and unresolved somatic postconcussive symptoms may be more likely to perceive various physical sensations throughout the body as painful and debilitating, ultimately seeking healthcare for these problems. Reporting these problems in primary care settings, these Veterans may then rapidly accumulate a variety of idiopathic complaints and other pain-related complaints in their medical records.

Clinical Implications and Recommendations

Although these results show that postconcussive symptoms are uniquely associated with health outcomes, they also demonstrate that postconcussive symptoms are strongly associated with PTSD. So, while Veterans with ongoing postconcussive symptoms may present to primary care settings reporting a variety of health complaints, these complaints are likely to occur in the context of psychosocial problems like PTSD. Thus, factors underlying these clinical presentations are likely multifaceted, and misattributing symptoms to one, unitary cause (e.g., a historical mTBI) may delay appropriate treatment referrals. Misattributing symptoms to a historical head injury may also inappropriately set up expectations for poor long-term prognosis. Therefore, clinicians treating Veterans with a history of mTBI and comorbid postconcussive and PTSD symptoms should be careful not to convey the message that physical and mental health complaints are the result of permanent brain damage associated with sustaining an mTBI. Doing so may lead to poor expectations regarding recovery and inadvertently enhance beliefs that mental and physical health will only deteriorate over time (Bryant et al., 2012).

However, these findings underscore the importance of thoroughly assessing for a history of deployment-related mTBIs and any current postconcussive symptoms, PTSD symptoms, and physical problems. Clinically, problems in one of these areas may well impact functioning in multiple domains (e.g., a Veteran presenting to primary care with a history of mTBI may present with various chronic pain complaints, including postconcussive headaches, that may exacerbate PTSD-related symptoms such as irritability and social withdrawal). Therefore, treating co-occurring postconcussive, PTSD, and physical symptoms likely requires a multidisciplinary approach. Bryant and colleagues (2012) recommend “treating what is treatable,” since improvements in one domain may well lead to improvements in postconcussive, PTSD, and physical problems.

From a multidisciplinary perspective, this may mean providing Veterans with referrals to clinics where they can receive specialized treatment for specific problems. Within the VA, referral to PTSD specialty clinics may be appropriate for treating PTSD symptoms, while VA or community sponsored exercise programs (e.g., VA’s MOVE Weight Management Program) may be helpful in targeting somatic/sensory postconcussive symptoms and idiopathic complaints. Bryant et al. (2012), for example, note that physical exercise has been associated with reductions in physical pain and headaches, as well as improved mood. Similarly, physical rehabilitation programs within the VA may help improve physical functioning and reduce physical symptoms. Some preliminary evidence also suggests that interventions targeting sleep and sleep hygiene (a nonspecific symptom associated with postconcussve syndrome and PTSD that is a commonly reported idiopathic health complaint) may help improve PTSD symptoms and postconcussive headache (see Otis et al., 2012, for review).

Clinicians working with these returning Veterans should be acutely sensitive to each Veteran’s unique clinical presentation and needs, making appropriate treatment referrals as needed. Coordination is also needed, however, to make sure that providers working in different clinics are tailoring specialized treatments for Veterans based on their clinical presentation and needs. Walker et al. (2010) proposed an integrated behavioral health care model for Veterans with postconcussive symptoms, PTSD, and health complaints whereby Veterans would be enrolled in what they call a

Postdeployment Multi-Symptom Disorder Program (PMDP). This program could function within the VA, and Veterans enrolled in this program would be triaged to specialty care clinics, such as TBI and Chronic Pain Rehabilitation clinics. PMDP staff would maintain contact with patients and specialty clinic staff as needed to ensure coordination of care, and Veterans in the program would also receive treatments for symptoms believed to be common to postconcussive syndrome, PTSD, and pain (e.g., disturbed sleep, coping deficits). Treatment components include psychoeducation, coping skills training, and cognitive-behavioral interventions for the management of postconcussive, PTSD, and pain symptoms. Since the efficacy of this integrated model of care has not been empirically established, future research is needed to determine the best way of delivering care to these Veterans with complex clinical presentations.

Study Limitations and Future Directions

While this study contributes to the evolving literature on relations between postconcussive symptoms, PTSD, and health, it is not without limitations. First, postconcussive and PTSD symptoms were assessed via self-report, which may bias overall symptom reporting. Second, it is not possible to fully determine whether postconcussive symptoms assessed on the NSI are indeed residual symptoms associated with a historical brain injury. Iverson (2012), for instance, has pointed out that a number of postconcussive symptoms, including headaches, irritability, and memory problems, may result from a number of conditions other than just brain injuries, an issue that he terms the “nonspecificity conundrum.” So, postconcussive symptoms assessed on the NSI, including somatic/sensory symptoms, may be associated with pre-deployment medical conditions or medical problems other than a historical mTBI. Similarly, it is not possible to determine whether clinician diagnosed health complaints assessed as part of the current study may reflect medical conditions with onset that predated deployment. Third, the data used for the current study preclude a full exploration of potential mechanisms underlying these results, and future studies are needed to address these important limitations. Fourth, we were not able to obtain data for the current study concerning any physical injuries sustained during OEF/OIF deployments that may contribute to overall disease burden.

In terms of future directions, longitudinal studies with multiple waves of data collection would help address whether the development of PTSD symptoms following an mTBI inhibits the resolution of postconcussive symptoms. The inclusion of neuropsychological tests in these longitudinal studies may also help address the role of neurocognitive functioning in the course of PTSD and postconcussive symptom development. Future studies may also wish to explore relations between postconcussive symptoms, PTSD, and other objective indicators of health, such as psychophysiological markers of health, in order to gain a more nuanced understanding of the long-term physical impact of comorbid postconcussive and PTSD symptoms. Furthermore, larger samples of Veterans with a history of deployment-related mTBI are needed in order to increase statistical power.

Conclusion

For many Veterans with persistent, postconcussive symptoms, these symptoms occur in the context of severe PTSD symptoms. Together, these symptoms may increase risk for a number of short- and long-term health problems. This study joins other recent studies (e.g., Vasterling et al., 2012) in suggesting that persistent postconcussive symptoms may have a unique impact on Veterans' health above and beyond that accounted for by PTSD, although PTSD likely plays an important role in the maintenance of these postconcussive symptoms. Therefore, this study serves as a call for both more basic research on the neuropathology underlying mTBI and persistent postconcussive symptoms, as well as more clinical research on efficacious treatments and treatment programs for Veterans presenting with this "postdeployment multi-symptom disorder."

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